# EXHIBIT B – PART C

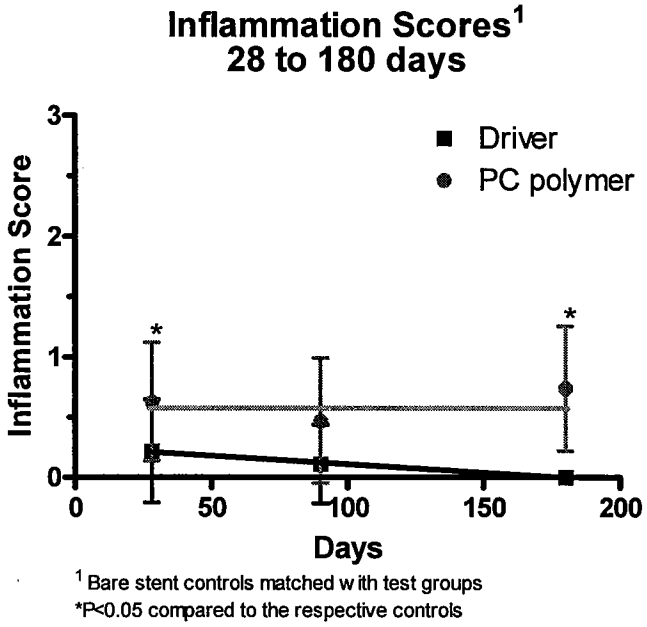


**Figure 4-10: Inflammation scores for PC polymer were consistently lower than 1 for time points ranging from 28 to 180 days without a trend in increasing sensitivity to polymer with time. Inflammatory response to polymer alone is no greater than that observed with the PC polymer-drug combination, indicating that drug was not masking the host response to polymer. Lines indicate the trend in inflammation response with time.**

Light microscopy revealed that the inflammatory response consisted mainly of mononuclear macrophages and giant cells around stent struts. Lymphocytes were rarely seen and eosinophils were not observed near the stent struts. The presence of eosinophils in these responses was highly exceptional and could only be observed as a minimal cellular component not associated with the stent or PC polymer in three sections covering up to 180 days of exposure. At 40x magnification, giant cells were seen in some cases around the struts at sites where deposits of basophilic material were observed. Further description of the material is provided in the following section, *Interaction of the Stent with the Adjacent Vessel Wall.*

A summary of the inflammatory response in swine is provided in Table 4-20 followed by a summary of the inflammatory response in rabbits in Table 4-21.

**Table 4-20: Swine Inflammatory Response (Score)[1] at the Site of Stent Implantation (Studies FS99, FS100, FS101, FS102 and FS135)**

| | Single Stents | | | | | | | | | | Overlapped Stents | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bare | 1ug | Bare | 5ug | Bare | 10ug | Bare | 30ug | Bare | Polymer | Bare | 10ug | Bare | 30ug |
| Day 7 Study FS102 | -- | -- | 1.17 ± 0.43 | 1.91 ± 0.16* | 1.33 ± 0.47 | 1.76 ± 0.25 | -- | -- | -- | -- | 1.40 ± 0.28 | 2.08 ± 0.42* | -- | -- |
| | -- | -- | n=4 | n=7 | n=4 | n=7 | -- | -- | -- | -- | n=5 | n=5 | -- | -- |
| Day 28 Study FS99 | 0.22 ± 0.43 | 0.53 ± 0.57* | 0.17 ± 0.38 | 0.85 ± 0.72* | 0.11 ± 0.32 | 0.67 ± 0.48* | 0.05 ± 0.22 | 0.59 ± 0.50* | 0.22 ± 0.43 | 0.63 ± 0.49* | 0.13 ± 0.35 | 0.84 ± 0.79* | 0.30 ± 0.47 | 0.93 ± 0.26* |
| | n=6 | n=10 | n=6 | n=9 | n=6 | n=9 | n=7 | n=9 | n=6 | n=10 | n=6 | n=10 | n=6 | n=9 |
| Day 90 Study FS100 | -- | -- | 0.00 ± 0.00 | 0.50 ± 0.52* | 0.00 ± 0.00 | 0.56 ± 0.62* | 0.08 ± 0.29 | 0.25 ± 0.45 | 0.11 ± 0.33 | 0.47 ± 0.52 | 0.63 ± 0.83 | 0.64 ± 0.93 | 0.00 ± 0.00 | 0.34 ± 0.48* |
| | -- | -- | n=5 | n=4 | n=4 | n=6 | n=4 | n=4 | n=3 | n=5 | n=4 | n=7 | n=4 | n=7 |
| Day 180 Study FS101 | -- | -- | 0.00 ± 0.00 | 0.58 ± 0.71 | 0.33 ± 0.47 | 0.86 ± 0.60 | 0.13 ± 0.18 | 0.38 ± 0.38 | 0.00 ± 0.00 | 0.74 ± 0.52* | 0.28 ± 0.30 | 1.13 ± 0.40* | 0.28 ± 0.30 | 0.31 ± 0.32 |
| | -- | -- | n=5 | n=8 | n=5 | n=7 | n=5 | n=8 | n=5 | n=9 | n=5 | n=9 | n=5 | n=7 |
| Day 28 Study FS135 | | | | | n=5 | n=10 | n=6 | n=10 | n=6 | n=10 | | | | |
| | NA | NA | NA | NA | 0.02 ± 0.08[2] | 1.73 ± 0.56 | 0.02 ± 0.08 | 1.23 ± 0.98 | 0.02 ± 0.08 | 0.10 ± 0.32 | NA | NA | NA | NA |

[1] Inflammation score
[2] Grouped control for 5 to 30 μg/mm doses
*p≤0.05 compared to the respective controls; -- not done

**Table 4-21: Rabbit Inflammatory Response (Score)[1] at the Site of Stent Implantation (Study FS107)**

| | Bare | 10 µg/mm |
|---|---|---|
| Day 7 | 2.14 ± 0.38 (n = 7) | 2.29 ± 0.76 (n = 7) |
| Day 28 | 0.00 ± 0.00 (n = 9) | 1.03 ± 0.43* (n = 9) |

[1] Inflammation score as described by Schwartz et al. (1992); *p<0.0001 compared to the respective controls

Porcine inflammation scores show mild response at all chronic time points up to 180 days with single and overlapped stents

**Interaction of the Stent with the Adjacent Vessel Wall**

No medial necrosis or thinning was observed in the swine studies for any of the single stents evaluated at Days 7, 28, 90, or 180 or for any of the overlapped stents evaluated at Days 7, 28, or 90. At 180 days the overlapped stents coated with 10 µg/mm of zotarolimus exhibited significantly greater medial thinning than the control overlapped stents (Study FS101). This was attributed to differential expansion of the stents at the time of placement rather than the drug coating since similar effects were not seen with overlapped stents coated with a higher concentration of zotarolimus (30µg/mm). Medial fractures or laceration by the stents were infrequently observed (i.e., semi-quantitative histology injury scores using the method of Schwartz et al.[39] were much less than 1), but were statistically higher for the Endeavor stent than the bare controls in some studies.

In addition, a study was conducted to specifically address the thrombogenic safety of the Endeavor Drug Eluting Stent System on various delivery system platforms (FS161) through evaluation of QCA and histomorphometry as compared to a bare metal Driver control group. All devices in this study were successfully delivered to the target site with no major device related complications and angiographic examination 11 days after implantation confirmed that all the stents had widely patent lumens without edge effect, aneurysm formation, filling defects or late thrombosis. All stented vessels had TIMI-3 flow. Morphometric evaluation showed that the Endeavor arms (RX, OTW and MX2) were statistically similar to the bare Driver control for intimal area, percent stenosis and intimal thickness. Histological evaluation showed that the Endeavor arms (RX, OTW and MX2) were statistically similar to bare Driver control in strut malapposition, percent struts with RBCs, percent endothelialization, inflammation score and percent granulomas. The bare metal Driver control showed statistically lower percent of struts with residual fibrin when compared to the three Endeavor arms as a consequence of drug action. No incidents of thrombosis or abnormal red blood cell extravasion were noted for any of the arms and the Endeavor stent was determined to be non-thrombogenic.

**PC Polymer**

The polymer portion of the drug-polymer layer of Endeavor may be left behind following drug elution. This is supported by the histopathological analysis of explanted porcine

[39] Schwartz, R.S., Huber, K.C., Murphy, J.G., Edwards, W.D., Camrud, A.R., Vlietstra, R.E., and Holmes, D.R. 1992. Restenosis and the proportional neointimal response to coronary artery injury: Results in a porcine model. J. Am. Coll. Cardiol. 19:267-274.

vessels from the Endeavor pre-clinical safety studies. This analysis found incidences of PC polymer, detectable as a basophilic deposit, adjacent to the stent struts that had been encapsulated in the neointima which is indicative of residual PC trapped between the stent and the vessel wall or on the abluminal surface of the strut. This material was seen as early as 7 days after implantation and was surrounded initially by giant cells and within 28 days by neointimal cells and matrix. This material was not seen protruding into the vessel lumens. There was minimal to no inflammatory response associated with these deposits. Further, no thrombotic events and >98% survival of the animals were seen in these studies. Thus, the residual PC polymer does not appear to adversely affect the safety of the stents.

**Fibrin Deposition**

Semi-quantitative histology scores for fibrin exhibited a decrease over time from average values of between 1.00 and 1.50 at Day 7 to average values of 0.00 by Day 90 (Table 4-22). Although no difference in fibrin scores was observed at 7 days after implantation (a time when fibrin scores were highest), by 28 days after implantation, the Endeavor stent had more residual fibrin than the bare control stents. The greater residual fibrin deposition observed with the zotarolimus-coated stents is similar to that seen with sirolimus-coated stents with the swine model (Suzuki et al. 2001). It is unknown whether the greater residual fibrin reflects a delay in arterial repair or impaired fibrin degradation secondary to the local effects of the drug. However, by 90 days after implantation, fibrin was no longer observed around either the control or drug-treated stents. Thus, no long-term effects on fibrin removal occurred with the Endeavor stent.

**Table 4-22: Fibrin Score[1] at the Site of Stent Implantation (Swine studies)**

| | Single Stents | | | | | | | | | | Overlapped Stents | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bare | 1 ug | Bare | 5 ug | Bare | 10 ug | Bare | 30 ug | Bare | Polymer | Bare | 10 ug | Bare | 30 ug |
| Day 7 FS102 | – | – | 1.00 ± 0.00 | 1.29 ± 0.49 | 1.25 ± 0.50 | 1.43 ± 0.54 | – | – | – | – | 1.80 ± 0.43 | 1.96 ± 0.36 | – | – |
| | – | – | n=4 | n=7 | n=4 | n=7 | – | – | – | – | n=5 | n=5 | – | – |
| Day 28 FS99 | 0.72 ± 0.46 | 1.00 ± 0.53 | 0.56 ± 1.42 | 1.22 ± 0.42* | 0.33 ± 0.49 | 1.15 ± 0.46* | 0.48 ± 0.51 | 0.96 ± 0.34* | 0.28 ± 0.46 | 0.27 ± 0.45 | 0.67 ± 0.48 | 1.46 ± 0.65* | 0.30 ± 0.47 | 1.00 ± 0.44 |
| | n=6 | n=10 | n=6 | n=9 | n=6 | n=9 | n=7 | n=9 | n=6 | n=10 | n=6 | n=10 | n=6 | n=9 |
| Day 90 FS100 | – | – | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.17 ± 0.38 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.18 ± 0.39* | 0.00 ± 0.00 | 0.00 ± 0.00 |
| | – | – | n=5 | n=4 | n=4 | n=6 | n=4 | n=4 | n=3 | n=5 | n=4 | n=7 | n=4 | n=7 |
| Day 180 FS101 | – | – | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.04 ± 0.12 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.06 ± 0.00 |
| | – | – | n=5 | n=8 | n=5 | n=7 | n=5 | n=8 | n=5 | n=9 | n=5 | n=9 | n=5 | n=7 |
| Day 28 FS135 (SVS) | | | | | n=10 | n=10 | n=10 | n=10 | n=10 | n=10 | | | | |
| | NA | NA | NA | NA | 0.02 ± 0.08[2] | 1.00 ± 1.25 | 0.02 ± 0.08[2] | 0.73 ± 1.21 | 0.02 ± 0.08[2] | 0.07 ± 0.21 | NA | NA | NA | NA |

[1] Fibrin score
[2] Grouped control for 5 to 30 μg/mm doses
*p<0.05 compared to the respective bare controls; – not done

Taken together the studies evaluating local tolerance and healing demonstrate that initially the stent produced a slightly greater level of inflammation surrounding stents than the bare control Driver stents. This effect was observed early after implantation but did not persist. Also, a slight delay in endothelialization and fibrin removal between overlapped bare and overlapped drug-coated stents was observed. However, no differences in long-term healing attributable to the presence of the drug coating on the stents was observed. Importantly, the slightly greater inflammation observed with the Endeavor stent did not result in greater levels of restentosis (see Pharmacodynamics, above).

**Endothelialization**

The effect of the stents on vascular endothelialization after stent placement was also evaluated by SEM in both swine and rabbits. At 7 days after implantation, vessels implanted with overlapping stents coated with 10 µg/mm of zotarolimus exhibited a lower degree of endothelialization (69% vs. 95% in the swine; 1.43% vs. 48.9% in the rabbit) than the bare Driver controls. However, single stents did not show a similar difference and at subsequent times after implantation (28, 90, and 180 days) in either swine or rabbits, all of the stents exhibited complete endothelialization at both the 90 and 180 day timepoints. Thus, the endothelium did not demonstrate any persistent inhibition of healing after implantation of the Endeavor stent.

As shown in Figure 4-11 below, porcine histology data shows rapid endothelial replacement with both single and overlapped stents.

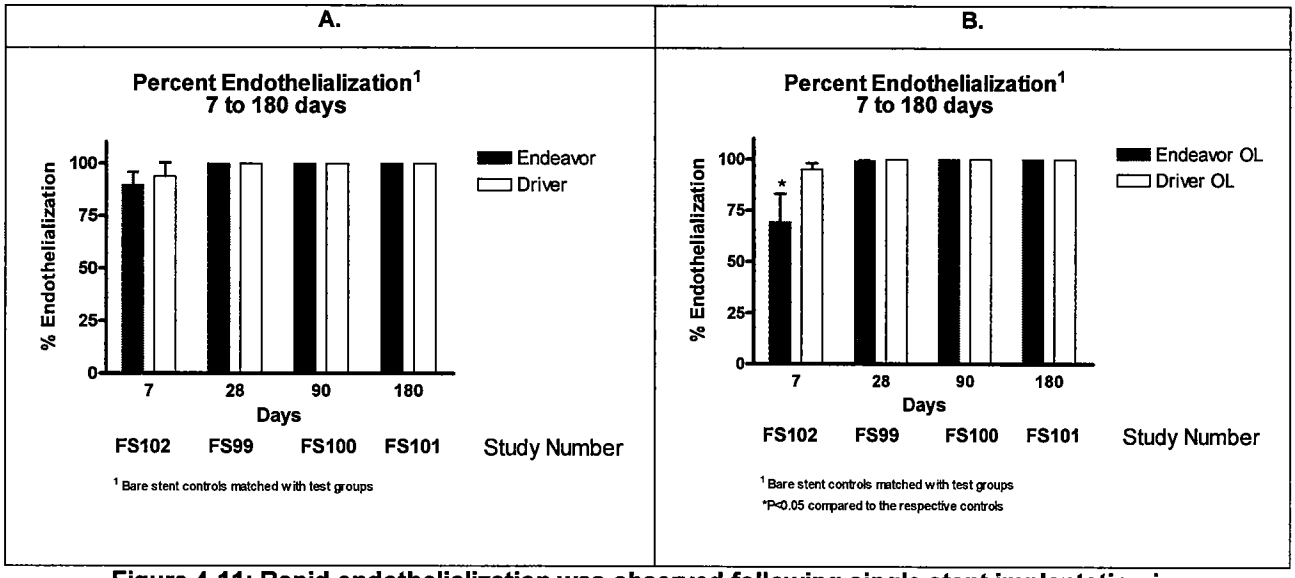


**Figure 4-11: Rapid endothelialization was observed following single stent implantation in the porcine model (A), with extensive coverage of the Endeavor stent observed within one week (not significantly different from Driver) and complete coverage at 28 days. Endothelialization of overlapped stents was delayed relative to Driver at 7 days (B) but complete at 28 days.**

Furthermore, as shown in Figure 4-12 below, porcine histology data shows rapid endothelial replacement with Endeavor 3X and 6X drug overdose using both single and overlapped stents.

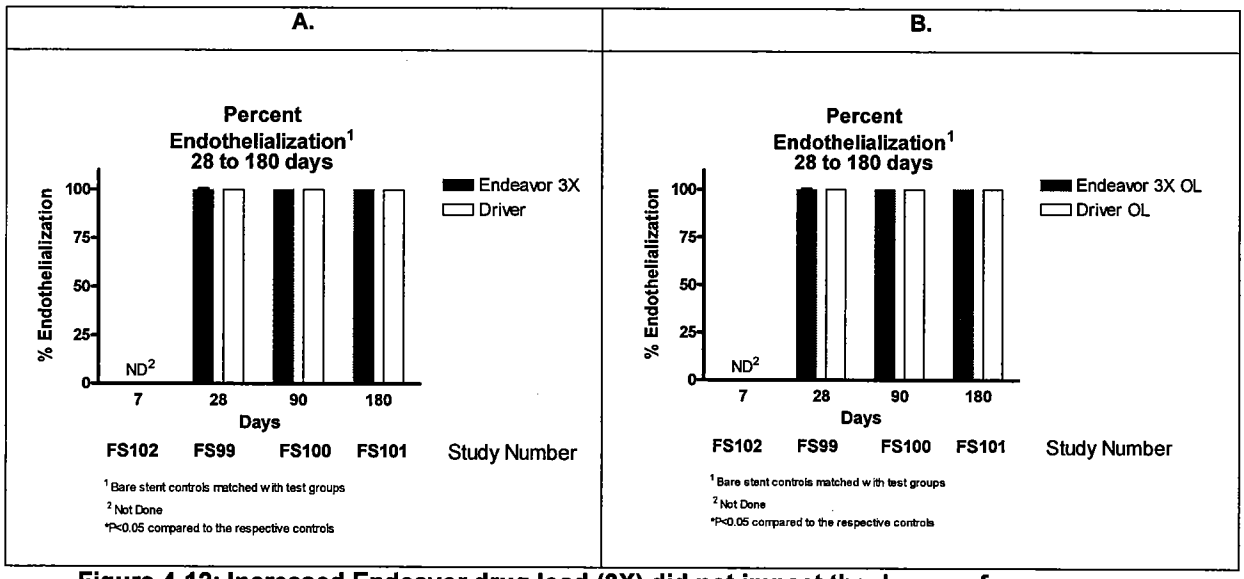


**Figure 4-12: Increased Endeavor drug load (3X) did not impact the degree of endothelialization observed with the Endeavor stent at 28 days or later time points relative to bare Driver stents in single stent implants (A), or with overlapped stents (B); 6X drug load within overlapped segments.**

The Endeavor Zotarolimus-Eluting CSS did not show a difference in rates of endothelialization when compared to BMS at 28, 90, and 180 days after implantation in either swine or rabbits, and exhibited complete endothelialization at both the 90 and 180 day time points.

**Endothelial Nitric Oxide Synthase**

Endothelial Nitric Oxide Synthase (eNOS) and the role of vessel function is one area of research Medtronic is conducting to better understand the safety profile of drug-eluting stents. Endothelial Nitric Oxide Synthase (eNOS) produces Nitric Oxide (NO), an important mediator for proper arterial vasodilation and an indicator of normal arterial function.

Medtronic Vascular has conducted research studies looking at eNOS levels after implantation with various drug-eluting stents including Endeavor. This research was presented at Transcatheter Cardiovascular Therapeutics (TCT) 2006. Cypher, Taxus, Endeavor and Driver stents were implanted in porcine coronary arteries. An acetylcholine challenge was conducted just prior to euthanasia and evaluated by QCA for diameter changes. Vessels were harvested at 28 and 90 days after stenting for the purpose of looking for the presence of eNOS in the stented vessels by immunohistochemistry and PCR probes. As a precursor to NO, the presence of high levels of eNOS was noted as indicating healthy xarterial function.

At 28 days in regions proximal to stent implantation as well as the in-stent segments of arteries, eNOS mRNA expression was greater for Endeavor than for Cypher and Taxus

(P<0.05) and similar to Driver. At 28 days, eNOS protein expression was strongly recognized in proximal regions of Endeavor- and Driver-implanted arteries but not in Cypher- and Taxus-implanted arteries. In the presence of an acetylcholine at 28 days, 6 of 7 Endeavor- and 13 of 15 Driver-implanted arteries showed vasodilation (normalization of endothelial function), whereas 7 of 9 Cypher - and 5 of 9 Taxus -implanted arteries showed vasoconstriction. These findings indicate rapid healing and normalization of endothelial function with the use on the Endeavor stent, potentially providing decreased risk of inflammation and thrombosis. At 90 days, however, all the stent-implanted arteries demonstrated vasodilation in the presence of an acetylcholine challenge, suggesting a similar level of healing was reached by this time point. At 90 days, in the region of the arteries proximal to the stents, eNOS mRNA expression was significantly greater for Endeavor than for Cypher ($P<0.05$) although the relative level of eNOS mRNA expression within the in-stent regions were greater for Cypher than for Endeavor and Taxus ($P<0.05$).

These findings suggest that rapid healing and normalization of endothelial function can be observed with the Endeavor stent at the 28 day time point in this model, potentially providing a mechanism for decreased risk of inflammation and thrombosis through NO production.

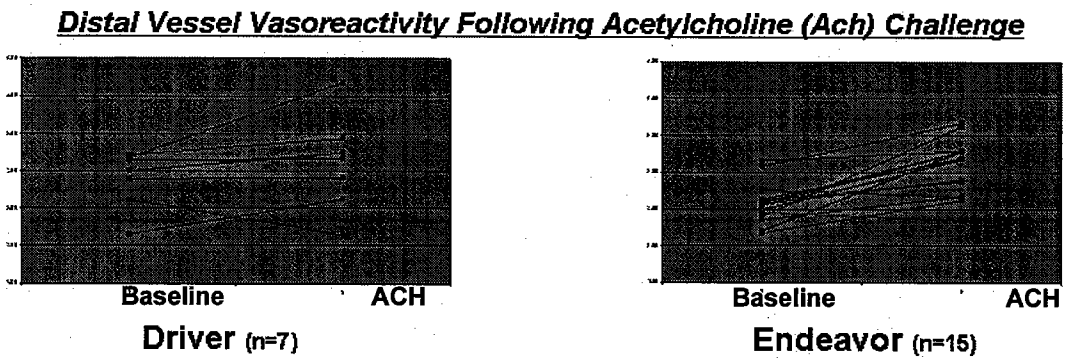


**Figure 4-13: Endeavor and Driver-implanted arteries showed vasodilation (normalization of endothelial function) following exposure to acetylcholine. These findings indicate rapid healing and restoration of endothelial function with the use on the Endeavor stent, potentially decreasing the risk of inflammation and thrombosis.**

### Myocardial Pathology

In addition to assessment of inflammation and injury to the vessel in which the stents had been placed, the myocardium of the swine was assessed for evidence of pathologic changes. Anterior, lateral, posterior, and septal sections were taken from both the apex and mid sections, and the sections were obtained from the area beneath the epicardial arteries. Few microscopic lesions related to presence of stents and no significant inflammatory changes were detected at 28, 90, or 180 days after implantation. Each of studies FS99, FS100, FS101, FS102, and FS110 included between 3% and 13% of animals with small myocardial vessels containing amorphous basophilic material with or without perivascular inflammatory cells. This material could also be seen as early as 11

days post-implant (FS161). In approximately half of the instances where the microemboli were observed, very small scars were observed in the myocardium adjacent to the vessels containing the material. Although, these findings were more numerous in the myocardium in the distribution of arteries implanted with Endeavor stents compared to control stents, additional studies suggest that these foreign body microemboli may be particles of the hydrophilic coating used on guidewires. The size of the amorphous basophilic fragments were quite small, and the clinical significance of the microemboli was thought to be minimal since none of the hearts examined exhibited gross lesions, and animal survival was >98%.

**Pre-clinical Conclusions**

In summary, the available data from studies submitted in the Endeavor Zotarolimus-Eluting CSS PMA has demonstrated:

- Drug safety and pharmacology
- Rapid, complete and functional endothelialization
- Low levels of drug/polymer induced inflammation and fibrin deposition
- No medial necrosis
- Low risk of thrombosis
- Broad margin of safety at 3x and 6x dose

Studies evaluating the elution of the drug, zotarolimus, from the Endeavor Zotarolimus-Eluting CSS after implantation demonstrate that the drug rapidly elutes from the stent, with less than 50% of the drug remaining on the stent at 24 hours after implantation and less than 6% remaining at 7 days. Blood levels rapidly decline to undetectable levels by 7 days after implantation and peripheral tissues have highly limited exposures. Thus, while systemic exposure is limited, drug remains at the implantation site for at least 28 days.

Overall it can be concluded that the stents performed as expected in the animal models, without evidence of increased toxicity due to the presence of the drug coating.

## 4.5 The Endeavor Clinical Program

The Endeavor Zotarolimus-Eluting Coronary Stent System clinical development program includes clinical safety and efficacy data from six multi-center trials conducted in the United States and abroad in support of PMA approval. Three of the six trials were randomized controlled studies and three were open-label trials. The randomized studies compared the safety and efficacy of the Endeavor stent to each of three marketed coronary stents: the uncoated bare metal Driver™ stent, the Cypher Sirolimus-Eluting Stent™, and the Taxus Paclitaxel-Eluting Coronary Stent System™. An additional registry was conducted in Japan to support regulatory approval in that country.

These studies provide extensive clinical safety and efficacy data for the Endeavor Zotarolimus-Eluting CSS. Among the PMA trials, 2,133 patients were assigned to receive the Endeavor stent and substantial follow up data is now available; 2,088 patients to 9 months, 1,301 patients to 12 months, 1,287 patients to 24 months, 675 patients to 36 months, and 97 patients to 48 months. Through randomized, controlled trials, the Endeavor stent was shown to be superior to a bare metal stent and non-inferior to a drug-eluting stent based on the composite endpoint of Target Vessel Failure (TVF). In addition, with substantial follow-up data available, there is no trend towards increased rates of cardiac death, MI, or stent thrombosis compared to the bare metal stent when assessed within the first year or in the critical post-one year time frame.

Table 4-23 below illustrates the key objective of each of the ENDEAVOR clinical trials. The subsequent section of this panel package provides additional details regarding each of these trials.

**Table 4-23: ENDEAVOR Trial Objectives**

| Trial | Trial Objective |
|---|---|
| ENDEAVOR I | First in-man / proof of concept |
| ENDEAVOR II | Double blind randomized controlled trial intended to prove superior clinical efficacy vs. BMS control and including a pharmacokinetic subset |
| ENDEAVOR II - CA | Open-label continued access registry until CE mark approval was granted, utilizing the same protocol as Endeavor II and allowing for direct stenting |
| ENDEAVOR III | Single-blind randomized controlled trial intended to confirm the results from the OUS ENDEAVOR II trial in a US population |
| ENDEAVOR IV | Single-blind randomized controlled trial intended to show non-inferiority to market leading US DES product |
| ENDEAVOR PK | Registry intended to evaluate pharmacokinetic properties in a US population |
| ENDEAVOR Japan | Registry intended to meet requirements for Japanese regulatory approval |

The strongest evidence for the safety and effectiveness is available from the three randomized controlled trials: ENDEAVOR II, ENDEAVOR III, and ENDEAVOR IV.

ENDEAVOR II was a double-blind randomized comparison to the currently marketed Driver bare metal stent. This OUS study was performed to determine if Endeavor produced significant reductions in re-intervention when compared to a BMS, as had been observed in previous DES vs. BMS trials. In this trial, Endeavor demonstrated superiority on the primary endpoint of Target Vessel Failure (TVF), a composite of cardiac death, Myocardial Infarction (MI), and Target Vessel Revascularization (TVR). In addition to demonstrating a significant reduction in TVF, statistically significant reductions in the secondary angiographic endpoints were also observed at 8 months. With three year follow-up now available, the reductions in clinical events seen at 9 months are preserved, and there is no increase in the critical events of stent thrombosis, cardiac death, or MI compared to the control. There has been no increase in revascularization compared to the bare metal stent from year one to year three. A more detailed discussion on the data supporting the safety and effectiveness of Endeavor is provided in Section 4.5.1 below.

ENDEAVOR III was a single-blind randomized comparison to the Cypher drug-eluting stent. The purpose of this trial was to confirm the results from the OUS ENDEAVOR II trial in a US population. An angiographic surrogate endpoint of in-segment late lumen loss was chosen as the primary endpoint, as it was believed to be correlated with clinical events. While the 8-month primary non-inferiority late lumen loss endpoint was not met, the TVF rate at 9 months was 11.8% for Endeavor vs. 11.5% for Cypher. Endeavor demonstrated a very low peri-procedural myocardial infarction rate. Although this trial was not powered to detect differences in clinical events, the only differences that have been demonstrated in follow-up out to two years have favored the Endeavor stent, driven by lower peri-procedural events.

ENDEAVOR IV was a single-blind randomized comparison to the Taxus drug-eluting stent. The purpose of the trial was to demonstrate non-inferiority to a marketed DES using an established clinical endpoint. The selected primary endpoint was the composite endpoint of TVF at 9 months, the same endpoint used in the ENDEAVOR II Trial. Clinical event rates were similar between Endeavor and Taxus based on non-inferiority being demonstrated for the primary clinical endpoint. While clinical rates were similar, it is interesting to note that differences were observed in terms of angiographic profiles between Endeavor and Taxus. The non-inferiority, powered secondary endpoint of in-segment late loss at 8 months was not demonstrated. Similar to ENDEAVOR III, the Endeavor stent also showed lower peri-procedural events compared to the Taxus stent.

These three trials provide a reasonable assurance of safety and effectiveness of the Endeavor system. No evidence of systemic toxicity was apparent in patients treated with the Endeavor Zotarolimus-Eluting CSS in clinical studies to date. In addition, there is no information indicating that the addition of zotarolimus leads to an increase in adverse events when compared to a placebo, a sirolimus-coated stent, or a paclitaxel-coated stent.

A summary of the major study characteristics of ENDEAVOR trials are provided in Table 4-24 below, followed by a summary of the key findings from this program. In addition, detailed summaries of each of the studies are provided in Section 6, and each of the final reports from the most recent follow-up are provided in the Appendices for reference.

**Table 4-24: Major Study Characteristics of ENDEAVOR Trials**

| | ENDEAVOR I | ENDEAVOR II | ENDEAVOR II-CA | ENDEAVOR III | ENDEAVOR IV | ENDEAVOR PK REGISTRY | ENDEAVOR JAPAN |
|---|---|---|---|---|---|---|---|
| **Study Description** | Multi-Center (8 OUS sites),<br>Non-Randomized | Multi-Center (72 OUS sites),<br>Prospective, Double-Blind, Randomized, Controlled | Multi-Center (15 OUS sites),<br>Prospective, Open-Label<br>Non-Randomized, Single Arm Continued Access Sub-Study | Multi-Center (29 US sites),<br>Prospective, Single-Blind, Parallel, Two-Arm, Randomized, Controlled | Multi-Center (80 US sites), Prospective, Single-Blind, Randomized, Two-Arm | Multi-Center (6 US sites), Prospective, Open-Label, Single Arm | Multi-center (11 Japan sites, Prospective, Open-Label, Single Arm |
| **Status** | Ongoing | Ongoing | Ongoing | Ongoing | Ongoing | Ongoing | Ongoing |
| **Follow-up Complete** | 48 months | 36 months | 24 Months | 24 Months | 9 Months | 9 Months | 9 Months |
| **Number of Patients** | 100 enrolled | 1197 enrolled | 296 enrolled | 436 enrolled | 1,548 enrolled | 43 enrolled | 99 enrolled |
| | 100 total patients with Endeavor Zotarolimus-Eluting CSS | 1:1 randomization to Endeavor Zotarolimus-Eluting CSS or Driver™ stents | 296 patients with Endeavor Zotarolimus-Eluting CSS | 3:1 randomization to Endeavor Zotarolimus-Eluting CSS or Cypher Sirolimus-Eluting Coronary Stent | 1:1 randomization to Endeavor Zotarolimus-Eluting CSS or Taxus Paclitaxel-Eluting Coronary Stent; patients stratified by diabetic status | 43 patients with Endeavor Zotarolimus-Eluting CSS | 99 patients with Endeavor Zotarolimus-Eluting CSS |
| **Lesion Criteria** | *De novo* lesion in native coronary artery, 3.0 to 3.5 mm in diameter, lesion coverable by one 18 mm stent | *De novo* lesion in native coronary artery >2.25 to <3.5 mm in diameter, and lesion lengths of ≥14 mm and ≤27 mm | *De novo* lesion in native coronary artery >2.25 to <3.5 mm in diameter, and lesion lengths of ≥14 mm and ≤27 mm | *De novo* lesion in native coronary artery >2.5 to <3.5 mm in diameter, and lesion lengths of ≥14 mm and ≤27 mm | *De novo* lesion in native coronary artery >2.5 to <3.5 mm in diameter, and lesion lengths of ≤27 mm | *De novo* lesions in native coronary artery >2.5 to <3.5 mm in diameter, and lesion lengths of ≤27 mm | *De novo* lesions in native coronary artery ≥2.5 to <3.5 mm in diameter, and lesion lengths of ≥14 mm and≤ 27 mm |

**Table 4-24: Major Study Characteristics of ENDEAVOR Trials**

| | ENDEAVOR I | ENDEAVOR II | ENDEAVOR II-CA | ENDEAVOR III | ENDEAVOR IV | ENDEAVOR PK REGISTRY | ENDEAVOR JAPAN |
|---|---|---|---|---|---|---|---|
| **Device Products Used** | Endeavor Zotarolimus-Eluting CSS, 3.0-3.5mm diameter, 18 mm length | Endeavor Zotarolimus-Eluting CSS, 2.25-3.5mm diameter and 8-30 mm in length or Driver Coronary Stent System | Endeavor Zotarolimus-Eluting CSS, 2.25-3.5mm diameter and 8-30 mm in length | Endeavor Zotarolimus-Eluting CSS, 2.5-3.5mm diameter and 8-30 mm in length or Cypher Sirolimus-Eluting Coronary Stent System | Endeavor Zotarolimus-Eluting CSS, 2.5-3.5mm diameter and 8-30 mm in length or Taxus Paclitaxel-Eluting Coronary Stent System | Endeavor Zotarolimus-Eluting CSS, 2.5-3.5mm diameter and 8-30 mm in length | Endeavor Zotarolimus-Eluting CSS, 2.5-3.5mm diameter and 8-30 mm in length |
| **Anti-platelet Therapy** | Aspirin indefinitely, and Ticlopidine or Clopidogrel for 12 weeks | Aspirin indefinitely, and Ticlopidine or Clopidogrel for 12 weeks | Aspirin indefinitely, and Ticlopidine or Clopidogrel for 12 weeks | Aspirin indefinitely, and Ticlopidine or Clopidogrel for minimum of 12 weeks | Aspirin indefinitely, and Ticlopidine or Clopidogrel for minimum of 6 months | Aspirin indefinitely, and Ticlopidine or Clopidogrel for minimum of 12 weeks | Aspirin indefinitely, and Ticlopidine for a minimum of 12 weeks |
| **Endpoints** | 1°:<br>30 day MACE and angiographic late lumen loss at 4 months | 1°:<br>Target vessel failure (TVF) rate at 9 months | 1°:<br>30 day MACE | 1°:<br>In-segment late lumen loss at 8 months | 1°:<br>Target vessel failure (TVF) rate at 9 months | 1°:<br>Pharmacokinetic parameters at 30 days. | 1°:<br>Target vessel failure (TVF) rate at 9 months |
| | 2°:<br>1) Target vessel failure (TVF);<br>2) Clinically-driven Target lesion revascularization (TLR) rate at 9 months;<br>3) Late lumen loss at 12 months as measured by angiography;<br>4) Neointimal hyperplastic volume at | 2°:<br>Lesion success, procedure success, device success, late lumen loss at 8 months, MACE at 30 days, 6, 9 and 12 months, TLR and Target vessel revascularization (TVR) at 9 months, angiographic in-stent and in-lumen diameter at 8 months, neointimal hyperplastic | 2°:<br>Device success, lesion success, procedure success, late lumen loss at 8 months, MACE at 30 days, 6, 9 and 12 months, in-stent and in-lesions binary restenosis rate at 8 months, angiographic in-stent and in-lumen diameter at 8 months, neointimal hyperplastic volume | 2°:<br>Device success, lesion success, procedure success, in-stent late lumen loss, target site revascularization (TSR) at 9 months, TVR and TVF at 9 months, angiographic binary restenosis (ABR) at 8 months, in-stent and in-segment minimum lumen diameter at 8 | 2°:<br>Device success, lesion success, procedure success, angiographic in-stent and in-segment percent diameter stenosis (%DS), late lumen loss, late loss index, angiographic binary restenosis rate, minimum luminal diameter at 8 months, neointimal hyperplastic volume and percent volume | 2°:<br>Device success, lesion success, procedure success for all patients<br>MACE at 30 days, 6, 9 and 12 months.<br>For patients receiving overlapping stents:<br>in-stent and in-segment percent diameter stenosis | 2°:<br>Device Success,<br>Lesion Success,<br>Procedure Success,<br>Major adverse cardiac events (MACE) – 30 days, 6 and 9 months post-procedure<br>Clinically-driven target lesion revascularization (TLR) – 9 months post-procedure,<br>Clinically-driven target |

**Table 4-24: Major Study Characteristics of ENDEAVOR Trials**

| | ENDEAVOR I | ENDEAVOR II | ENDEAVOR II-CA | ENDEAVOR III | ENDEAVOR IV | ENDEAVOR PK REGISTRY | ENDEAVOR JAPAN |
|---|---|---|---|---|---|---|---|
| | baseline, 4, and 12 months by IVUS. | volume at 8 months by IVUS, TLR at 8 months, PK analyses | at 8 months by IVUS, TVR and TVF at 9 months. | months, neointimal hyperplastic volume at 8 months by IVUS | obstruction (%VO) at 8 months by IVUS, target site revascularization (TSR) rate and TVR at 9 months | (%DS), late lumen loss, late loss index, angiographic binary restenosis (ABR) rate, minimum luminal diameter, neointimal hyperplastic volume and percent volume obstruction (%VO) at 8 months by IVUS, target site revascularization (TSR), TVF and TVR at 9 months | vessel revascularization (TVR) – 9 months post-procedure,<br>In stent and in segment late loss – 8 months post-procedure (measured by Quantitative Coronary Angiography [QCA]),<br>In stent and in segment binary angiographic restenosis (50% diameter or more stenosis) – 8 months post-procedure (measured by QCA),<br>In stent and in segment minimal lumen diameter (MLD) – 8 months post-procedure (measured by QCA) |

The ENDEAVOR clinical program was established to demonstrate the safety and effectiveness of this new DES system in patients with progressively greater levels of clinical complexity. The initial feasibility study (ENDEAVOR I) conducted in Australia and New Zealand was limited to a group of patients in whom the treated arteries were relatively low-risk (e.g., 3.0-3.5 mm in diameter, discrete or tubular (<15 mm), coverable by a single 18 mm length stent). In the ENDEAVOR I study, history of hypertension and/or diabetes were modest, 53% and 16%, respectively. Based on excellent results in ENDEAVOR I, the subsequent trials were designed to include patients with smaller vessel diameters and greater lesion lengths. The double-blind, randomized controlled trial against the Driver stent (ENDEAVOR II) included a more complicated group of patients, including subjects with smaller native arteries (the 2.25 mm diameter stent was included), longer stented lesions (up to 27 mm per protocol), greater frequency of ≥20 mm lesions (15%), more complex B2 (53%) and C (26%) class lesions, and a slightly larger subset of patients with hypertension (66%) or diabetes (20%). The subsequent single-blind, randomized controlled US trials against Cypher (ENDEAVOR III) and Taxus (ENDEAVOR IV) stents retained or exceeded the level of complexity of the subjects seen in ENDEAVOR II, while the open-label continued access trial ENDEAVOR II-CA was even more challenging, including a majority of patients with history of hypertension (82%), a large subset with diabetes (26%), and the most complex lesions (27% ≥20 mm and 44% class C lesions). In addition, this continued access study also allowed for direct stenting of lesions < 20 mm in length at physicians' discretion. The ENDEAVOR Japan study was a 99-patient registry conducted to meet requirements for Japanese regulatory approval.

The clinical utility of the Endeavor Zotarolimus-Eluting CSS was established in each of the studies with remarkably consistent results across studies. All quantitative results (e.g., angiographic and intravascular ultrasound data) from the ENDEAVOR I, II, IICA, III, IV, and PK studies were evaluated in the same highly-experienced core laboratories in the US (Brigham and Women's Angiographic Core Laboratory and Stanford University Cardiovascular Intravascular Ultrasound Core Laboratory, respectively), ensuring a high level of consistency for these critical analyses. This consistency in data analysis across the entire dataset of patients receiving the Endeavor Zotarolimus-Eluting CSS is an important feature in interpreting the entire body of clinical data, and especially in supporting the utility of data from experience outside of the US. With only minor exceptions, the clinical studies also consistently incorporated a standard patient assessment schedule for the key core evaluations, thus ensuring reproducible evaluations of: 1) acute success parameters; 2) standard nine-month outcomes related to extent of restenosis; and 3) long-term clinical safety and efficacy related to freedom from stent failure.

The acute success parameters relate to stent deliverability. Overall, lesion and device success rates were excellent across the studies of the Endeavor Zotarolimus-Eluting CSS, in the range of 97-100% for over 2,100 recipients. Procedure success rates were similarly high for all studies, with only a slightly lower procedure success in the ENDEAVOR II-CA study (94.9%) which is expected due to a greater number of complex lesions and higher risk patients than other Endeavor trials. Delivery of the Endeavor Zotarolimus-Eluting CSS was compelling in comparison to patients receiving either the Cypher stent

in ENDEAVOR III or the Taxus stent in ENDEAVOR IV. Procedure success rates were higher with the Endeavor stent compared to the Cypher stent (99.4% vs 95.6%) or the Taxus stent (98.7% vs 96.8%). The Endeavor Zotarolimus-Eluting CSS was associated with a lower incidence of peri-procedural non-Q wave myocardial infarctions in both ENDEAVOR III (0.6% vs 3.5%) and ENDEAVOR IV (0.5% vs 2.2%). This significant difference in non-Q wave myocardial infarctions drove the difference in procedure success in both trials.

Randomized clinical comparison of the efficacy of the Endeavor Zotarolimus-Eluting CSS to marketed drug-eluting stents provided the first head-to-head evaluation of the DES and their clinical performance in the United States. The large multi-center randomized comparisons of the Endeavor Zotarolimus-Eluting CSS and the Cypher Sirolimus-Eluting Stent (ENDEAVOR III) or Taxus Paclitaxel-Eluting Stent (ENDEAVOR IV) enrolled nearly 2,000 patients with coronary artery lesions to include lesions between 2.5 mm and 3.5 mm in diameter and up to 27 mm in length. ENDEAVOR III and IV present a unique opportunity to evaluate safety results that are directly comparable due to randomization. In addition, ENDEAVOR III and ENDEAVOR IV represent a new era in drug-eluting stent trials (a shift towards non-inferiority comparisons) which help to elucidate the relationship between angiographic parameters and clinical outcomes.

Comparison of the Endeavor Zotarolimus-Eluting CSS to the Cypher stent in ENDEAVOR III provided Endeavor clinical data in a US population. Acute success (discussed above) and 30-day MACE rates favored the Endeavor Zotarolimus-Eluting CSS over the Cypher stent, with an in-hospital MACE rate of 0.6% in the Endeavor arm vs. 3.5% in the Cypher arm.. At later time points, the two groups demonstrated generally similar efficacy based on rates of MACE, target lesion or vessel revascularization, or target vessel failure during nine-month, 12 month or 24 month follow-up evaluations, recognizing that the study was underpowered for these endpoints. The designated primary endpoint of in-segment late lumen loss at eight months was significantly higher among patients treated with Endeavor Zotarolimus-Eluting CSS versus the Cypher stent ($0.36\pm0.46$ mm vs. $0.13\pm0.33$mm, $p<0.001$), corresponding to a higher frequency of in-segment binary restenosis (12.3% vs. 4.3%). It is noteworthy that the in-segment late loss value of the Cypher stent was lower than the observed values in other recent Cypher stent clinical trials.[40,41,42]

A significant objective in designing the ENDEAVOR III clinical trial was to determine if the angiographic and clinical results seen with the Endeavor Zotarolimus-Eluting CSS in this US clinical trial were harmonious with those from previous international clinical trials assessing Endeavor Zotarolimus-Eluting CSS. Angiographic outcomes for the

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[40] Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.

[41] Morice, M-C., Serruys, P.W., Sousa, J.E., Fajadet, J., Hayashi, E.B., Perin, M., Colombo, A., *et al.* "A Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization." *New England Journal of Medicine* 346(23):1773-1781 (2002).

[42] Morice, M-C., Colombo, A., Meier, B., Serruys, P., Tamburino, C., Guagliumi, G., Sousa, E., Stoll, H-P. "Sirolimus – vs Paclitaxel-Eluting Stents in De Novo Coronary Artery Lesions." *Journal of the American Medical Association* 295(8):895-904 (2006).

Endeavor Zotarolimus-Eluting CSS in the ENDEAVOR III trial were virtually identical to those observed in the ENDEAVOR II, indicating that the performance of the Endeavor Zotarolimus-Eluting CSS was consistent in randomized trials conducted abroad (ENDEAVOR II) and in the US (ENDEAVOR III). The subsequent ENDEAVOR IV trial further confirmed the consistency of these outcomes. Reference Table 4-25 below for the angiographic outcomes across trials.

**Table 4-25: Consistency Across Randomized Trials**

| | ENDEAVOR II | ENDEAVOR III | ENDEAVOR IV |
|---|---|---|---|
| **Follow up** | 8 months | 8 months | 8 months |
| **In-segment late loss (n)** | 0.36±0.46 (246) | 0.36 mm ±0.46 (277) | 0.36 mm ±0.47 (143) |
| **% diameter stenosis (n)** | 32.67±16.27 (264) | 30.42±15.57 (277) | 32.28±17.02 (144) |
| **Binary in-segment restenosis** | 13.3% (35/264) | 12.3% (34/277) | 15.3% (22/144) |

These angiographic parameters were lower than the BMS in ENDEAVOR II and higher than Cypher in ENDEAVOR III and Taxus in ENDEAVOR IV. Specifically, the in-segment late loss values for the Driver, Cypher and Taxus arms were 0.72 mm, 0.13 mm, and 0.23 mm, respectively. While Endeavor's angiographic profile is different from those of the other DES products, Endeavor has sufficiently controlled neointimal proliferation to sustain good clinical outcomes as evidenced by superior clinical outcomes compared to Driver and non-inferior clinical outcomes compared to Taxus.

### 4.5.1 Safety and Effectiveness

The ideal drug eluting stent should provide for superior clinical efficacy compared to bare metal stents with equivalent safety as measured by cardiac death, myocardial infarction (MI) and stent thrombosis.

In a PMA clinical program comprised of six multi-center trials, 2,133 patients assigned to receive the Endeavor stent, and 675 patients followed to three years, it has been shown that the Endeavor DES is both safe and effective and provides a net patient benefit. Endeavor significantly reduces the need for repeat revascularization vs. the Driver bare metal stent (BMS) and exhibits a long-term clinical efficacy rate that is similar to the currently available DES.

In addition, Endeavor exhibits a safety profile that may be unique among other drug eluting stents:

- Lower rates of cardiac death and MI vs. BMS based on FDA-requested post hoc, pooled analysis
- An overall rate of stent thrombosis no different than the BMS
- Numerically lower rates of periprocedural MI vs. two DES controls

The collective evidence provides assurance that Endeavor is both safe and effective.

**Effectiveness**

The efficacy profile of Endeavor can be characterized as follows:

- Endeavor shows statistically superior clinical efficacy vs. the BMS control in ENDEAVOR II; this treatment effect is sustained out to three years of follow-up.
- Endeavor shows statistically non-inferior efficacy vs. the Taxus control stent at 9 months in ENDEAVOR IV. At 24 months, the TVF rate was 14.4% for Endeavor and 13.4% for Cypher in ENDEAVOR III.

*Statistical improvement in clinical efficacy vs. the BMS control.*

In the ENDEAVOR II trial, as shown in Table 4-26, Endeavor demonstrated clear superiority against the Driver BMS for the composite primary endpoint of Target Vessel Failure (TVF).

**Table 4-26: ENDEAVOR II Primary Endpoint**

| | Endeavor | Driver Control | Difference [95% CI] | P value |
|---|---|---|---|---|
| Target Vessel Failure to 270 days | 7.9% (47/592) | 15.1% (89/591) | -7.1% [-10.7%,-3.5%] | <0.001 |

The dramatic reduction in TVF was largely driven by the reduced need for revascularization as measured by Target Lesion Revascularization (TLR). As shown in Table 4-27 below, the significant reduction in TLR vs. the BMS control has been shown to be sustained over time.

**Table 4-27: ENDEAVOR II TLR Over Time**

| | Endeavor (N=598 patients) | Driver (N=599 patients) | Difference [95% CI]* |
|---|---|---|---|
| Target Lesion Revascularization to 270 days | 4.6% (27/592) | 11.8% (70/591) | -7.3% [-10.4%,-4.2%] |
| Target Lesion Revascularization to 360 days | 5.9% (35/590) | 13.1% (77/589) | -7.1% [-10.5%,-3.8%] |
| Target Lesion Revascularization to 720 days | 6.5% (38/587) | 14.2% (83/586) | -7.7% [-11.1%,-4.2%] |
| Target Lesion Revascularization to 1080 days | 7.3% (42/577) | 14.7% (85/579) | -7.4% [-11.0%,-3.8%] |

* Unadjusted for multiple comparisons

*Endeavor exhibits a long-term clinical efficacy rate that is similar to the currently available products.*

The ENDEAVOR IV trial was the first head-to-head randomized controlled trial comparing two DES using a clinical primary endpoint, Target Vessel Failure (TVF). In

the ENDEAVOR IV trial, as shown in Table 4-28, Endeavor demonstrated clear non-inferiority to the market-leading Taxus Paclitaxel-Eluting Coronary Stent System.

**Table 4-28: ENDEAVOR IV Primary Endpoint**

| | Endeavor | TAXUS Control | Difference [One-sided 95% CI] | P value* |
|---|---|---|---|---|
| Target Vessel Failure to 270 days | 6.8% (50/740) | 7.4% (54/734) | -0.6% [-100%, 1.6%] | 0.0005 |

*P-value is for the test of Non-Inferiority.

In addition to the primary endpoint, as shown in Table 4-29, the rates for other major clinical endpoints in ENDEAVOR IV were also similar for Taxus and Endeavor groups.

**Table 4-29: ENDEAVOR IV Major Clinical Endpoint Results at 9 months**

| | Endeavor | Taxus | Difference [95% CI]* |
|---|---|---|---|
| **Death** | 0.7% (5/740) | 0.8% (6/734) | -0.1% [-1.0%, 0.7%] |
| **Cardiac Death** | 0.4% (3/740) | 0.3% (2/734) | 0.1% [-0.5%, 0.7%] |
| **MI** | 1.5% (11/740) | 2.5% (18/734) | -1.0% [-2.4%, 0.5%] |
| **Q-wave MI** | 0.3% (2/740) | 0.1% (1/734) | 0.1% [-0.3%, 0.6%] |
| **Non Q-wave MI** | 1.2% (9/740) | 2.3% (17/734) | -1.1% [-2.4%, 0.2%] |
| **TLR** | 4.2% (31/740) | 2.7% (20/734) | 1.5% [-0.4%, 3.3%] |
| **TVR** | 5.5% (41/740) | 5.0% (37/734) | 0.5% [-1.8%, 2.8%] |
| **Stent thrombosis** | | | |
| **Protocol** | 0.8% (6/740) | 0.1% (1/734) | *** |
| **ARC definite + probable**** | 0.9% (7/740) | 0.1% (1/734) | *** |

* Unadjusted for multiple comparisons

** Reported ARC rates are uncensored and include events that occured both before and after TLR events

*** Confidence intervals are only provided for components of the primary endpoint.

ENDEAVOR III provided for an angiographic comparison to the other marketed DES, the Cypher Sirolimus-Eluting Coronary Stent System. ENDEAVOR III was not powered to evaluate clinical endpoints. TVF results are shown in Table 4-30 for reference.

**Table 4-30: ENDEAVOR III TVF**

| | Endeavor | CYPHER Control |
|---|---|---|
| Target Vessel Failure to 270 days | 11.8% (38/321) | 11.5% (13/113) |
| Target Vessel Failure to 360 days | 12.8% (41/320) | 11.6% (13/112) |
| Target Vessel Failure to 720 days | 14.4% (45/313) | 13.4% (15/112) |

Protocol-mandated angiographic follow-up led to a slight increase in TLR as reported at 9 months. This was consistently demonstrated across each of the randomized trials. As shown in Table 4-31 through Table 4-33 below, for patients in ENDEAVOR II and ENDEAVOR IV with angiographic follow-up, the 270 day TLR rate ranged from 5.7% to 6.9% compared to patients with clinical follow-up who had TLR rates ranging from 3.5% to 3.7%.

**Table 4-31: Angiographic vs. Clinical Follow-up TLR (ENDEAVOR II)**

| | Angiographic Follow-up | | Clinical only Follow-up | |
|---|---|---|---|---|
| | Endeavor N=264 | Driver N=265 | Endeavor N=334 | Driver N=334 |
| TLR at 270 days | 5.7% (15/264) | 16.2% (43/265) | 3.7% (12/328) | 8.3% (27/326) |

**Table 4-32: Angiographic vs. Clinical Follow-up TLR (ENDEAVOR III*)**

| | Angiographic Follow-up | | Clinical only Follow-up | |
|---|---|---|---|---|
| | Endeavor N=277 | Cypher N=94 | Endeavor N=46 | Cypher N=19 |
| TLR at 270 days | 6.7% (19/277) | 4.3% (4/94) | 2.3% (2/44) | 0.0% (0/19) |

* All patients were scheduled to receive angiographic follow-up in ENDEAVOR III

**Table 4-33: Angiographic vs. Clinical Follow-up TLR (ENDEAVOR IV)**

| | Angiographic Follow-up | | Clinical only Follow-up | |
|---|---|---|---|---|
| | Endeavor N=144 | Taxus N=135 | Endeavor N=629 | Taxus N=640 |
| TLR at 270 days | 6.9% (10/144) | 3.0% (4/133) | 3.5% (21/596) | 2.7% (16/601) |

## Safety

As mentioned in the opening comments in this section, the ideal drug eluting stent should not only exhibit superior efficacy as compared to a BMS, but it should also exhibit equivalent safety as measured by stent thrombosis, cardiac death, and MI. In both head-to-head comparisons of Endeavor vs. Driver in ENDEAVOR II and in the post-hoc pooled analysis requested by FDA (ENDEAVOR I, II, IICA, III, IV and PK vs. Driver), Endeavor exhibits an equivalent or better safety profile than the bare metal control. As demonstrated in Table 4-34, in Endeavor II, at both the 9 month timepoint and the 36 month timepoint, Endeavor shows rates of death, MI, and stent thrombosis that are not statistically different from the Driver BMS control.

**Table 4-34: ENDEAVOR II Clinical Measures at 270 and 1080 Days**

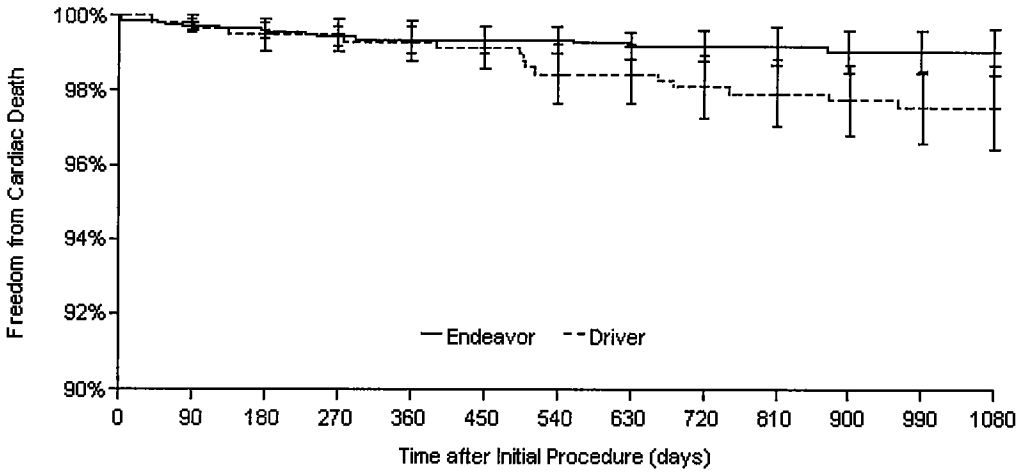
| | 270 days | | | 1080 days | | |
|---|---|---|---|---|---|---|
| | Endeavor | Driver Control | Difference [95% CI]* | Endeavor | Driver Control | Difference [95% CI]* |
| **TVF Rate** | 7.9% (47/592) | 15.1% (89/591) | -7.1% [-10.7%,-3.5%] | 12.8% (74/577) | 21.4%(124/579) | -8.6% [-12.9%,-4.3%] |
| **Death** | 1.2%(7/592) | 0.5%(3/591) | 0.7% [-0.4%,1.7%] | 3.3% (19/577) | 4.5% (26/579) | -1.2% [-3.4%,1.0%] |
| **Cardiac Death** | 0.8%(5/592) | 0.5%(3/591) | 0.3% [-0.6%,1.3%] | 1.6% (9/577) | 2.4% (14/579) | -0.9%[-2.5%,0.8%] |
| **MI** | 2.7%(16/592) | 3.9%(23/591) | -1.2% [-3.2%,0.8%] | 3.3% (19/577) | 4.3%(25/579) | -1.0% [-3.2%,1.2%] |
| **Q-wave MI** | 0.3%(2/592) | 0.8%(5/591) | -0.5% [-1.4%,0.4%] | 0.3% (2/577) | 1.0%(6/579) | -0.7% [-1.6%,0.3%] |
| **Non Q-wave MI** | 2.4%(14/592) | 3.0%(18/591) | -0.7% [-2.5%,1.2%] | 2.9% (17/577) | 3.3% (19/579) | -0.3% [-2.3%,1.7%] |
| **TLR** | 4.6%(27/592) | 11.8%(70/591) | -7.3% [-10.4%,-4.2%] | 7.3% (42/577) | 14.7%(85/579) | -7.4% [-11.0%,-3.8%] |
| **TVR** | 5.6%(33/592) | 12.5%(74/591) | -6.9% [-10.2%,-3.7%] | 9.5% (55/577) | 17.6%(102/579) | -8.1% [-12.0%,-4.2%] |
| **Stent thrombosis** | | | | | | |
| **Protocol** | 0.5%(3/592) | 1.2%(7/591) | *** | 0.5% (3/577) | 1.2% (7/579) | *** |
| **ARC definite + probable **** | 0.5%(3/592) | 1.4%(8/591) | *** | 0.9% (5/577) | 1.6% (9/579) | *** |

* Unadjusted for multiple comparisons

** Reported ARC rates are uncensored and include events that occured both before and after TLR events

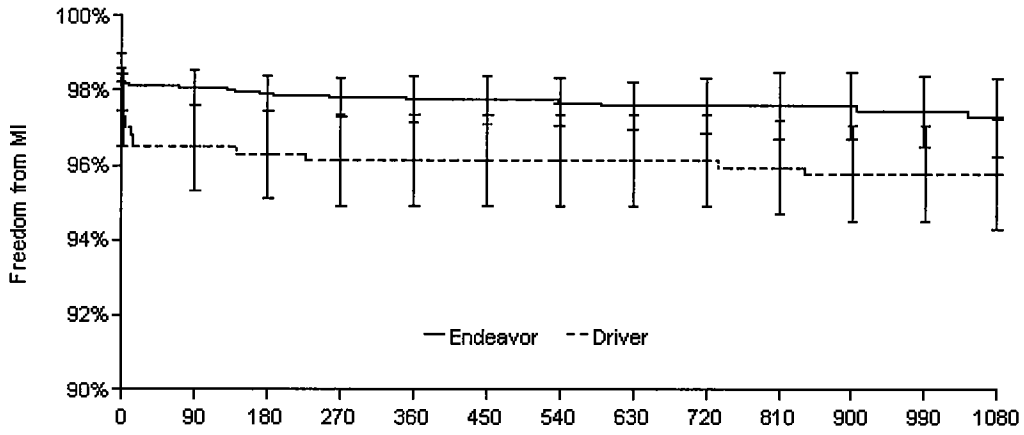
*** Confidence intervals are only provided for components of the primary endpoint.

Moreover, when examining the FDA-requested pooled Endeavor data set vs. the BMS control, the safety trends shown in the ENDEAVOR II trial are further demonstrated. As shown in this post hoc analysis provided in Figure 4-14 through Figure 4-16below, at three years, Endeavor shows lower critical event rates of cardiac death, MI, and combined cardiac death and MI compared to Driver.



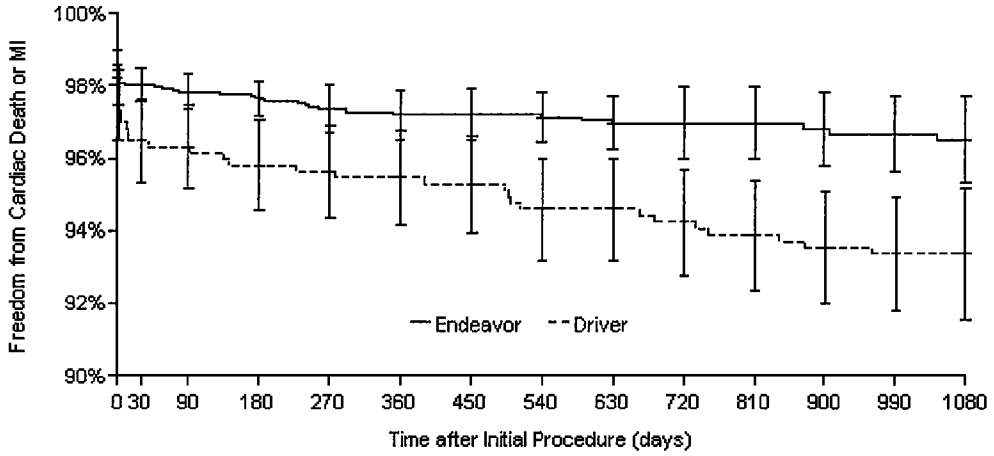

| Cardiac Death | 0 | 30 | 90 | 180 | 270 | 360 | 450 | 540 | 630 | 720 | 810 | 900 | 990 | 1080 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Endeavor** | | | | | | | | | | | | | | |
| # Entered | 2132 | 2132 | 2116 | 2103 | 2090 | 1291 | 1278 | 1261 | 1256 | 1251 | 665 | 655 | 653 | 651 |
| # Censored | 0 | 13 | 10 | 11 | 795 | 12 | 17 | 5 | 3 | 586 | 10 | 1 | 2 | 121 |
| # Incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| # Events | 0 | 3 | 3 | 2 | 4 | 1 | 0 | 0 | 2 | 0 | 0 | 1 | 0 | 0 |
| % Survived | 100.0% | 99.9% | 99.7% | 99.6% | 99.4% | 99.4% | 99.4% | 99.4% | 99.2% | 99.2% | 99.2% | 99.0% | 99.0% | 99.0% |
| SE | 0.0% | 0.1% | 0.1% | 0.1% | 0.2% | 0.2% | 0.2% | 0.2% | 0.3% | 0.3% | 0.3% | 0.4% | 0.4% | 0.4% |
| **Driver** | | | | | | | | | | | | | | |
| # Entered | 596 | 596 | 594 | 592 | 588 | 583 | 576 | 572 | 568 | 568 | 562 | 557 | 555 | 551 |
| # Censored | 0 | 2 | 1 | 2 | 5 | 6 | 3 | 0 | 0 | 4 | 4 | 1 | 3 | 134 |
| # Incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| # Events | 0 | 0 | 1 | 2 | 0 | 1 | 1 | 4 | 0 | 2 | 1 | 1 | 1 | 0 |
| % Survived | 100.0% | 100.0% | 99.8% | 99.5% | 99.5% | 99.3% | 99.1% | 98.5% | 98.5% | 98.1% | 97.9% | 97.8% | 97.6% | 97.6% |
| SE | 0.0% | 0.0% | 0.2% | 0.3% | 0.3% | 0.3% | 0.4% | 0.5% | 0.5% | 0.6% | 0.6% | 0.6% | 0.6% | 0.7% |
| **Tests Between Groups** | | | | | | | | | | | | | | |
| | Test | Chi-Square | Deg Frdm | P Value | | | | | | | | | | |
| | Log-Rank | 5.00 | 1 | 0.025 | | | | | | | | | | |
| | Wilcoxon | 2.89 | 1 | 0.089 | | | | | | | | | | |

**Figure 4-14: Survival Free from Cardiac Death to 1080 Days**




| MI | 0 | 30 | 90 | 180 | 270 | 360 | 450 | 540 | 630 | 720 | 810 | 900 | 990 | 1080 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Endeavor** | | | | | | | | | | | | | | |
| # Entered | 2132 | 2102 | 2077 | 2063 | 2048 | 1259 | 1246 | 1230 | 1224 | 1219 | 649 | 639 | 637 | 634 |
| # Censored | 0 | 12 | 9 | 10 | 780 | 11 | 15 | 1 | 1 | 570 | 7 | 0 | 0 | 113 |
| # Incomplete | 0 | 3 | 4 | 2 | 7 | 1 | 1 | 4 | 3 | 0 | 3 | 2 | 2 | 2 |
| # Events | 30 | 10 | 1 | 3 | 2 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 |
| % Survived | 98.6% | 98.1% | 98.1% | 97.9% | 97.8% | 97.8% | 97.8% | 97.7% | 97.6% | 97.6% | 97.6% | 97.6% | 97.4% | 97.3% |
| SE | 0.3% | 0.3% | 0.3% | 0.3% | 0.4% | 0.4% | 0.4% | 0.4% | 0.4% | 0.6% | 0.6% | 0.6% | 0.6% | 0.7% |
| **Driver** | | | | | | | | | | | | | | |
| # Entered | 596 | 581 | 573 | 571 | 566 | 560 | 553 | 549 | 545 | 545 | 539 | 534 | 532 | 528 |
| # Censored | 0 | 2 | 1 | 2 | 5 | 6 | 2 | 0 | 0 | 3 | 2 | 0 | 1 | 123 |
| # Incomplete | 0 | 0 | 1 | 2 | 0 | 1 | 2 | 4 | 0 | 3 | 2 | 1 | 3 | 5 |
| # Events | 15 | 6 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| % Survived | 97.5% | 96.5% | 96.5% | 96.3% | 96.1% | 96.1% | 96.1% | 96.1% | 96.1% | 96.1% | 96.0% | 95.8% | 95.8% | 95.8% |
| SE | 0.6% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.9% | 0.9% | 1.0% |
| **Tests Between Groups** | | | | | | | | | | | | | | |
| | Test | Chi-Square | Deg Frdm | P Value | | | | | | | | | | |
| | Log-Rank | 3.93 | 1 | 0.047 | | | | | | | | | | |
| | Wilcoxon | 4.57 | 1 | 0.033 | | | | | | | | | | |

**Figure 4-15: Survival Free from MI to 1080 Days**




| Cardiac Death or MI | 0 | 30 | 90 | 180 | 270 | 360 | 450 | 540 | 630 | 720 | 810 | 900 | 990 | 1080 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Endeavor** | | | | | | | | | | | | | | |
| # Entered | 2132 | 2102 | 2077 | 2063 | 2048 | 1259 | 1246 | 1230 | 1224 | 1219 | 649 | 639 | 637 | 634 |
| # Censored | 0 | 12 | 9 | 10 | 780 | 11 | 15 | 1 | 1 | 570 | 7 | 0 | 0 | 113 |
| # Incomplete | 0 | 1 | 1 | 1 | 3 | 0 | 1 | 4 | 2 | 0 | 3 | 1 | 2 | 2 |
| # Events | 30 | 12 | 4 | 4 | 6 | 2 | 0 | 1 | 2 | 0 | 0 | 1 | 1 | 1 |
| % Survived | 98.6% | 98.0% | 97.8% | 97.6% | 97.4% | 97.2% | 97.2% | 97.1% | 97.0% | 97.0% | 97.0% | 96.8% | 96.7% | 96.5% |
| SE | 0.3% | 0.3% | 0.3% | 0.3% | 0.4% | 0.5% | 0.5% | 0.5% | 0.5% | 0.7% | 0.7% | 0.7% | 0.7% | 0.8% |
| **Driver** | | | | | | | | | | | | | | |
| # Entered | 596 | 581 | 573 | 571 | 566 | 560 | 553 | 549 | 545 | 545 | 539 | 534 | 532 | 528 |
| # Censored | 0 | 2 | 1 | 2 | 5 | 6 | 2 | 0 | 0 | 3 | 2 | 0 | 1 | 123 |
| # Incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 2 | 5 |
| # Events | 15 | 6 | 1 | 3 | 1 | 1 | 1 | 4 | 0 | 2 | 2 | 2 | 1 | 0 |
| % Survived | 97.5% | 96.5% | 96.3% | 95.8% | 95.6% | 95.5% | 95.3% | 94.6% | 94.6% | 94.2% | 93.9% | 93.5% | 93.4% | 93.4% |
| SE | 0.6% | 0.8% | 0.8% | 0.8% | 0.8% | 0.9% | 0.9% | 0.9% | 0.9% | 1.0% | 1.0% | 1.0% | 1.0% | 1.2% |
| **Tests Between Groups** | | | | | | | | | | | | | | |
| | Test | Chi-Square | Deg Frdm | P Value | | | | | | | | | | |
| | Log-Rank | 9.80 | 1 | 0.002 | | | | | | | | | | |
| | Wilcoxon | 8.44 | 1 | 0.004 | | | | | | | | | | |

**Figure 4-16: Survival Free from Cardiac Death or MI at 1080 Days**

For the critical safety endpoint of stent thrombosis, Endeavor rates have been reported using two different reporting mechanisms: the pre-specified protocol definition and the retrospective Academic Research Consortium (ARC) event rates. Regardless of the method for reporting, both the randomized ENDEAVOR II comparison and the FDA-requested pooled analysis have shown Endeavor to have low event rates that are similar to or lower than the Driver BMS. The ENDEAVOR II stent thrombosis rates at 270 days and 1080 days are provided in Table 4-35 below.

**Table 4-35: ENDEAVOR II Stent Thrombosis Rates***

| | 270 days | | 1080 days | |
|---|---|---|---|---|
| | Endeavor | Driver Control | Endeavor | Driver Control |
| **Protocol** | 0.5%(3/592) | 1.2%(7/591) | 0.5% (3/577) | 1.2% (7/579) |
| **ARC definite + probable** | 0.5%(3/592) | 1.4%(8/591) | 0.9% (5/577) | 1.6% (9/579) |

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events

Similarly, upon examination of the pre-specified protocol definition and the more conservative uncensored ARC definitions, the pooled comparison provided in Table 4-36 continues to show no increase in stent thrombosis events for the Endeavor stent compared to the Driver stent.

**Table 4-36: Pooled Stent Thrombosis***

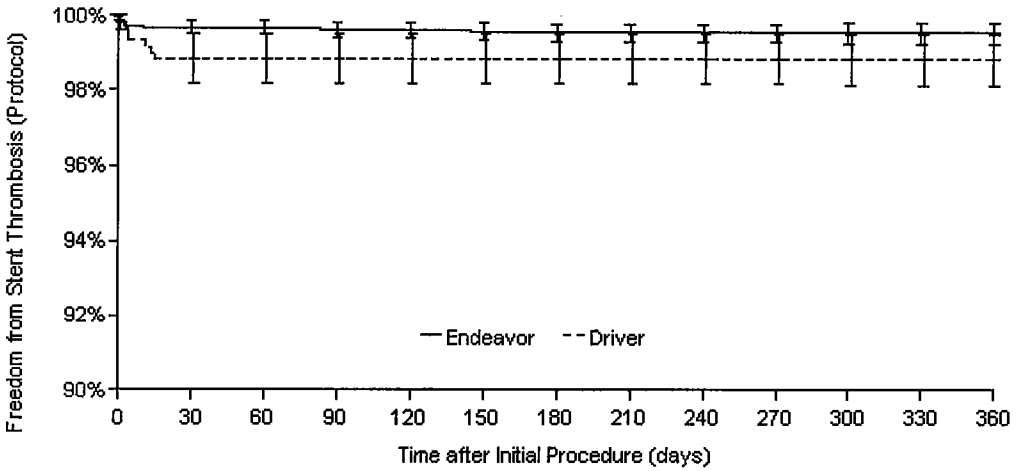
| | Endeavor (N=2132) | 95% CI | Driver (N=596) | 95% CI |
|---|---|---|---|---|
| **Thrombosis (0-30 days)** | | | | |
| Stent Thrombosis (Protocol) | 0.3% (7/2128) | [0.1%,0.7%] | 1.2% (7/594) | [0.5%,2.4%] |
| ARC Definite Plus Probable | 0.3% (7/2128) | [0.1%,0.7%] | 1.2% (7/594) | [0.5%,2.4%] |
| **Thrombosis (0-180 days)** | | | | |
| Stent Thrombosis (Protocol) | 0.5% (10/2118) | [0.2%,0.9%] | 1.2% (7/593) | [0.5%,2.4%] |
| ARC Definite Plus Probable | 0.5% (11/2118) | [0.3%,0.9%] | 1.2% (7/593) | [0.5%,2.4%] |
| **Thrombosis (0-360 days)** | | | | |
| Stent Thrombosis (Protocol) | 0.3%(4/1301) | [0.1%,0.8%] | 1.2% (7/589) | [0.5%,2.4%] |
| ARC Definite Plus Probable | 0.5% (6/1301) | [0.2%,1.0%] | 1.4% (8/589) | [0.6%,2.7%] |
| **Thrombosis (0-720 days)** | | | | |
| Stent Thrombosis (Protocol) | 0.3%(4/1287) | [0.1%,0.8%] | 1.2% (7/586) | [0.5%,2.4%] |
| ARC Definite Plus Probable | 0.5% (7/1287) | [0.2%,1.1%] | 1.4% (8/586) | [0.6%,2.7%] |
| **Thrombosis (0-1080 days)** | | | | |
| Stent Thrombosis (Protocol) | 0.6%(4/675) | [0.2%,1.5%] | 1.2% (7/579) | [0.5%,2.5%] |
| ARC Definite Plus Probable | 0.9% (6/675) | [0.3%,1.9%] | 1.6% (9/579) | [0.7%,2.9%] |

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events

When comparing the rates of stent thrombosis, it is important to analyze the timing of stent thrombosis events. It has been reported that the timing of stent thrombosis events with currently available drug-eluting stents appears to be different from that of bare metal stents, with a numerical increase in the frequency of very late stent thrombosis.[43]

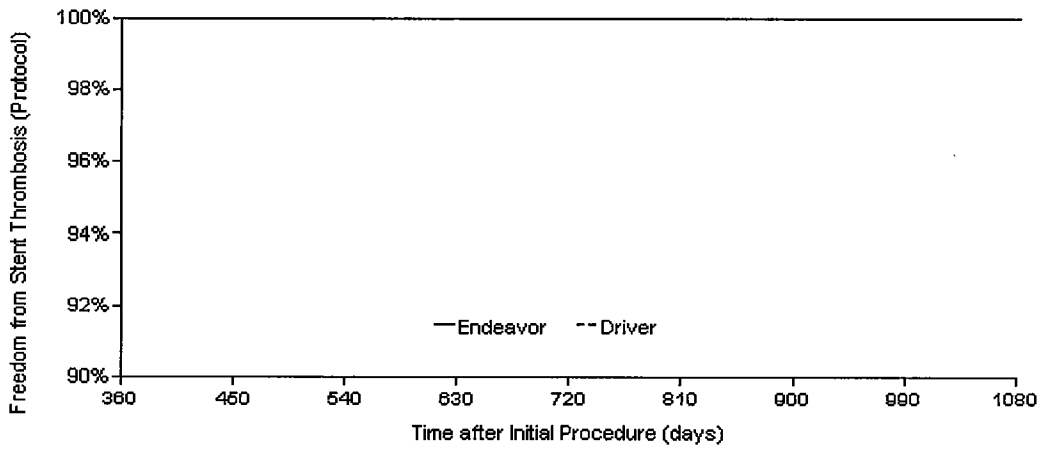
[43] Laskey WK, Yancy CW, Maisel WH, Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medical Devices Advisory Panel of the Food and Drug Administration Center for Devices and Radiologic Health, December 7-8, 2006. Circulation. 2007 May 1;115(17):2352-7.

The rates of stent thrombosis in the Endeavor program were analyzed prior to six months and after six months, as well as prior to one year and after one year in order to determine if there was an increase in late events. When examining stent thrombosis, at each interval analyzed, Endeavor exhibits a rate of stent thrombosis that is no different from that of the Driver bare metal stent. Beyond one year, the Endeavor stent showed zero stent thrombosis by the pre-specified protocol definition, and there was one event in both Endeavor and Driver arms of the ENDEAVOR II clinical trial by the *post hoc* ARC definition (definite plus probable). The pre- and post-one-year stent thrombosis rates are provided in Figure 4-17 through Figure 4-20 below.



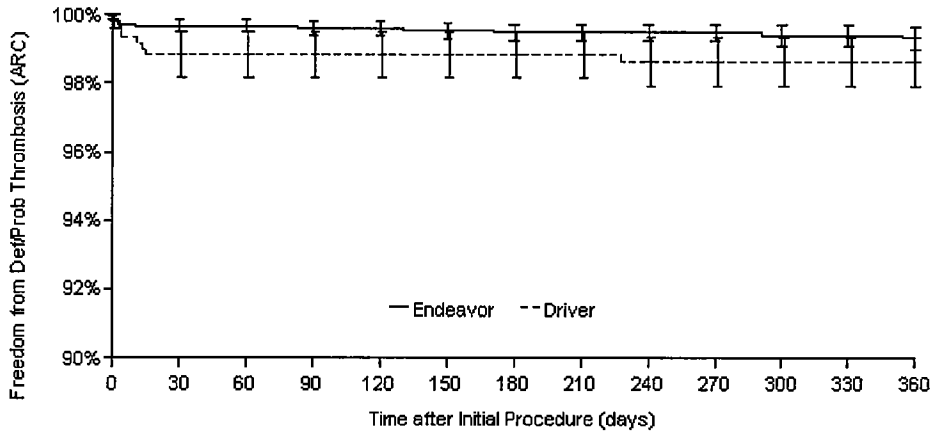

| Stent Thrombosis (Protocol) | 0 | 30 | 60 | 90 | 120 | 150 | 180 | 210 | 240 | 270 | 300 | 330 | 360 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Endeavor** | | | | | | | | | | | | | |
| # Entered | 2132 | 2131 | 2111 | 2100 | 2097 | 2097 | 2094 | 2082 | 2074 | 2065 | 1918 | 1283 | 1278 |
| # Censored | 0 | 12 | 8 | 1 | 0 | 0 | 10 | 7 | 7 | 143 | 634 | 5 | 3 |
| # Incomplete | 0 | 2 | 3 | 1 | 0 | 2 | 1 | 1 | 2 | 4 | 1 | 0 | 0 |
| # Events | 1 | 6 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| % Survived | 100.0% | 99.7% | 99.7% | 99.6% | 99.6% | 99.6% | 99.5% | 99.5% | 99.5% | 99.5% | 99.5% | 99.5% | 99.5% |
| SE | 0.0% | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% |
| **Driver** | | | | | | | | | | | | | |
| # Entered | 596 | 595 | 587 | 586 | 585 | 584 | 582 | 581 | 580 | 580 | 576 | 570 | 570 |
| # Censored | 0 | 2 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 4 | 5 | 0 | 1 |
| # Incomplete | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| # Events | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % Survived | 99.8% | 98.8% | 98.8% | 98.8% | 98.8% | 98.8% | 98.8% | 98.8% | 98.8% | 98.8% | 98.8% | 98.8% | 98.8% |
| SE | 0.2% | 0.4% | 0.4% | 0.4% | 0.4% | 0.4% | 0.4% | 0.4% | 0.4% | 0.4% | 0.4% | 0.4% | 0.4% |
| **Tests Between Groups** | | | | | | | | | | | | | |
| | Test | Chi-Square | Deg Frdm | P-value | | | | | | | | | |
| | Log-Rank | 3.73 | 1 | 0.053 | | | | | | | | | |
| | Wilcoxon | 3.75 | 1 | 0.053 | | | | | | | | | |

**Figure 4-17: Survival Free from Stent Thrombosis (Protocol) Prior to 360 Days**




| Stent Thrombosis (Protocol) | 360 | 450 | 540 | 630 | 720 | 810 | 900 | 990 | 1080 |
|---|---|---|---|---|---|---|---|---|---|
| **Endeavor** | | | | | | | | | |
| # Entered | 1278 | 1278 | 1261 | 1256 | 1251 | 1008 | 655 | 653 | 651 |
| # Censored | 0 | 16 | 1 | 1 | 242 | 350 | 0 | 0 | 119 |
| # Incomplete | 0 | 1 | 4 | 4 | 1 | 3 | 2 | 2 | 2 |
| # Events | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % Survived | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| SE | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| **Driver** | | | | | | | | | |
| # Entered | 576 | 576 | 572 | 568 | 568 | 562 | 557 | 555 | 551 |
| # Censored | 0 | 2 | 0 | 0 | 3 | 2 | 0 | 1 | 129 |
| # Incomplete | 0 | 2 | 4 | 0 | 3 | 3 | 2 | 3 | 5 |
| # Events | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % Survived | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| SE | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| **Tests Between Groups** | | | | | | | | | |
| | Test | Chi-Square | Deg Frdm | P-value | | | | | |
| | Log-Rank | 0.00 | 0 | – | | | | | |
| | Wilcoxon | 0.00 | 0 | – | | | | | |

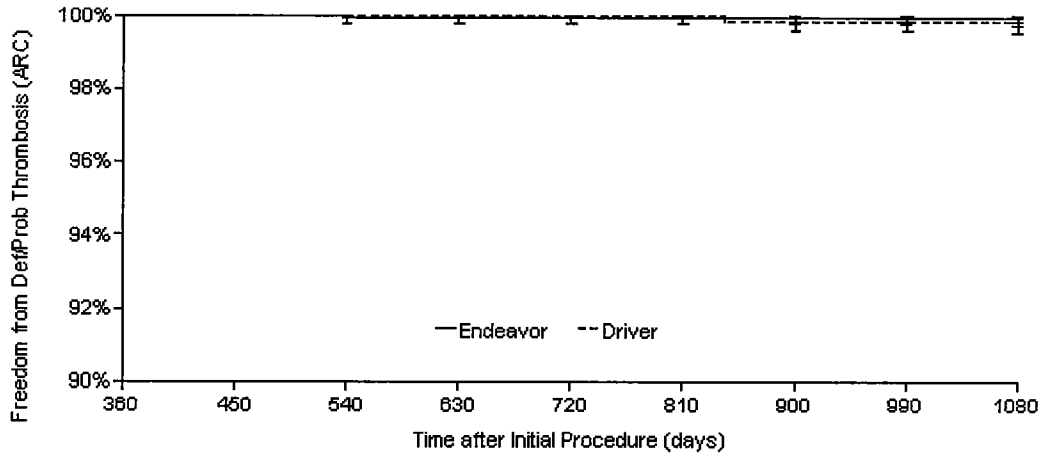
**Figure 4-18: Survival Free from Stent Thrombosis (Protocol) between 361 and 1080 Days**




| Def/Prob Thrombosis (ARC) | 0 | 30 | 60 | 90 | 120 | 150 | 180 | 210 | 240 | 270 | 300 | 330 | 360 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Endeavor** | | | | | | | | | | | | | |
| # Entered | 2132 | 2131 | 2111 | 2100 | 2097 | 2097 | 2093 | 2081 | 2073 | 2064 | 1917 | 1283 | 1278 |
| # Censored | 0 | 12 | 8 | 1 | 0 | 0 | 10 | 7 | 7 | 143 | 633 | 5 | 3 |
| # Incomplete | 0 | 2 | 3 | 1 | 0 | 2 | 1 | 1 | 2 | 4 | 0 | 0 | 0 |
| # Events | 1 | 6 | 0 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 1 | 0 | 1 |
| % Survived | 100.0% | 99.7% | 99.7% | 99.6% | 99.6% | 99.5% | 99.5% | 99.5% | 99.5% | 99.5% | 99.4% | 99.4% | 99.3% |
| SE | 0.0% | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% |
| **Driver** | | | | | | | | | | | | | |
| # Entered | 596 | 595 | 587 | 586 | 585 | 584 | 582 | 581 | 580 | 579 | 575 | 569 | 569 |
| # Censored | 0 | 2 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 4 | 5 | 0 | 1 |
| # Incomplete | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| # Events | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| % Survived | 99.8% | 98.8% | 98.8% | 98.8% | 98.8% | 98.8% | 98.8% | 98.8% | 98.7% | 98.7% | 98.7% | 98.7% | 98.7% |
| SE | 0.2% | 0.4% | 0.4% | 0.4% | 0.4% | 0.4% | 0.4% | 0.4% | 0.5% | 0.5% | 0.5% | 0.5% | 0.5% |
| **Tests Between Groups** | | | | | | | | | | | | | |
| | Test | Chi-Square | Deg Frdm | P-value | | | | | | | | | |
| | Log-Rank | 2.86 | 1 | 0.091 | | | | | | | | | |
| | Wilcoxon | 3.42 | 1 | 0.064 | | | | | | | | | |

**Figure 4-19: Survival Free from Def/Prob Thrombosis (ARC) Prior to 360 Days***

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events




| Def/Prob Thrombosis (ARC) | 360 | 450 | 540 | 630 | 720 | 810 | 900 | 990 | 1080 |
|---|---|---|---|---|---|---|---|---|---|
| **Endeavor** | | | | | | | | | |
| # Entered | 1278 | 1278 | 1261 | 1255 | 1251 | 1008 | 655 | 653 | 651 |
| # Censored | 0 | 16 | 1 | 1 | 242 | 350 | 0 | 0 | 119 |
| # Incomplete | 0 | 1 | 4 | 3 | 1 | 3 | 2 | 2 | 2 |
| # Events | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| % Survived | 100.0% | 100.0% | 99.9% | 99.9% | 99.9% | 99.9% | 99.9% | 99.9% | 99.9% |
| SE | 0.0% | 0.0% | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% |
| **Driver** | | | | | | | | | |
| # Entered | 576 | 576 | 572 | 568 | 568 | 562 | 557 | 554 | 550 |
| # Censored | 0 | 2 | 0 | 0 | 3 | 2 | 0 | 1 | 129 |
| # Incomplete | 0 | 2 | 4 | 0 | 3 | 3 | 2 | 3 | 5 |
| # Events | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| % Survived | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 99.8% | 99.8% | 99.8% |
| SE | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.2% | 0.2% | 0.2% |
| **Tests Between Groups** | | | | | | | | | |
| | Test | Chi-Square | Deg Frdm | P-value | | | | | |
| | Log-Rank | 0.11 | 1 | 0.737 | | | | | |
| | Wilcoxon | 0.01 | 1 | 0.934 | | | | | |

**Figure 4-20: Survival Free from Definite/Probable Thrombosis (ARC) between 361 and 1080 Days***
* Reported ARC rates are uncensored and include events that occurred both before and after TLR events

Diabetes has been a patient population of interest with drug-eluting stents.[44] Post-hoc subset analyses have been performed at the FDA's request to assess the outcomes of patients with diabetes. As shown in Table 4-37, for the pooled Endeavor patients, there were no increases in the rates of death, cardiac death, MI, or stent thrombosis among all diabetics or insulin or non-insulin dependent diabetics. There was an expected increase in the rates of TLR and TVR among diabetics.

**Table 4-37: Diabetes - Pooled Endeavor Clinical Events at 270 Days**

| | Non-Diabetics N=1549 | All Diabetics N=537 |
|---|---|---|
| Death | 0.8% (12/1522) | 0.8% (4/521) |
| Cardiac Death | 0.5% (7/1522) | 0.6% (3/521) |
| MI | 2.4% (37/1522) | 1.5% (8/521) |
| Cardiac Death or MI | 2.8% (43/1522) | 1.9% (10/521) |
| Protocol ST | 0.5% (7/1522) | 0.6% (3/521) |
| Definite and Probable ST (ARC)* | 0.5% (7/1522) | 0.8% (4/521) |
| TLR | 4.1% (62/1522) | 6.3% (33/521) |
| TVR | 5.8% (89/1522) | 9.4% (49/521) |
| | **Non-Diabetics N=1549** | **Insulin-Dependent N=154** |
| Death | 0.8% (12/1522) | 0.7% (1/150) |
| Cardiac Death | 0.5% (7/1522) | 0% (0/150) |
| MI | 2.4% (37/1522) | 2% (3/150) |
| Cardiac Death or MI | 2.8% (43/1522) | 2% (3/150) |
| Protocol ST | 0.5% (7/1522) | 0.7% (1/150) |
| Definite and Probable ST (ARC)* | 0.5% (7/1522) | 1.3% (2/150) |
| TLR | 4.1% (62/1522) | 6% (9/150) |
| TVR | 5.8% (89/1522) | 8% (12/150) |
| | **Non-Diabetics N=1549** | **Non-Insulin-Dependent N=381** |
| Death | 0.8% (12/1522) | 0.8% (3/369) |
| Cardiac Death | 0.5% (7/1522) | 0.8% (3/369) |
| MI | 2.4% (37/1522) | 1.4% (5/369) |
| Cardiac Death or MI | 2.8% (43/1522) | 1.9% (7/369) |
| Protocol ST | 0.5% (7/1522) | 0.5% (2/369) |
| Definite and Probable ST (ARC)* | 0.5% (7/1522) | 0.5% (2/369) |
| TLR | 4.1% (62/1522) | 6.5% (24/369) |
| TVR | 5.8% (89/1522) | 9.8% (36/369) |

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events

[44] Pinto Slottow TL, Waksman R, Overview of the 2006 Food and Drug Administration Circulatory System Devices Panel meeting on drug-eluting stent thrombosis. Catheter Cardiovasc Interv. 2007 Jun 1;69(7):1064-74.

In addition, the clinical event rates for diabetic patients from the pooled Endeavor studies and the diabetic Driver patients from ENDEAVOR II are also provided. These data show no increase in the rates of death, cardiac death, MI, or stent thrombosis with Endeavor compared to Driver.

**Table 4-38: Diabetes – Pooled Endeavor Clinical Events and Driver at 270 Days**

| | Endeavor N=537 | Driver N=132 |
|---|---|---|
| Death | 0.8% (4/521) | 1.5% (2/132) |
| Cardiac Death | 0.6% (3/521) | 1.5% (2/132) |
| MI | 1.5% (8/521) | 3.8% (5/132) |
| Cardiac Death or MI | 1.9% (10/521) | 5.3% (7/132) |
| Protocol ST | 0.6% (3/521) | 2.3% (3/132) |
| Definite and Probable ST (ARC)* | 0.8% (4/521) | 2.3% (3/132) |
| TLR | 6.3% (33/521) | 15.2% (20/132) |
| TVR | 9.4% (49/521) | 15.9% (21/132) |

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events

The clinical event rates for Endeavor and Taxus patients in the randomized ENDEAVOR IV study are also provided which show no demonstrated increase in the rates of death, cardiac death, MI, or stent thrombosis with Endeavor compared to Taxus.

**Table 4-39: Diabetes – ENDEAVOR IV Clinical Events at 270 Days**

| | Endeavor N=241 | Taxus N=236 |
|---|---|---|
| Death | 0% (0/227) | 0.4% (1/223) |
| Cardiac Death | 0% (0/227) | 0.4% (1/223) |
| MI | 0.9% (2/227) | 0.9% (2/223) |
| Cardiac Death or MI | 0.9% (2/227) | 1.3% (3/223) |
| Protocol ST | 0.9% (2/227) | 0.4% (1/223) |
| Definite and Probable ST (ARC)* | 1.3% (3/227) | 0.4% (1/223) |
| TLR | 6.2% (14/227) | 5.8% (13/223) |
| TVR | 7.9% (18/227) | 7.6% (17/223) |

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events

Interim data is also available from an Endeavor OUS postmarket registry. After commercialization of the Endeavor Zotarolimus-Eluting Coronary Stent System (CSS) outside the United States (US), Medtronic initiated the Endeavor-FIVE (E-FIVE) post approval study to continue to monitor safety and performance in the commercial market place. Approximately 200 centers located in Europe, Asia, Australia, New Zealand and South America enrolled over 8000 patients into this registry. Patient enrollment started in September 2005 and is currently ongoing. There were 2015 patients enrolled through March 16, 2006 at 73 centers. Per FDA's request, an interim report was compiled with 30-day data on the first 2000 patients enrolled into the study and submitted in the original PMA for Endeavor. In addition, one year data is now available from the first approximately 1000 patients enrolled in the study. The interim E-FIVE data presented below in Table 4-40 at one year demonstrates low rates of critical events in the

postmarket setting. The pooled Endeavor rates from the analysis described above are also provided for reference.

**Table 4-40: Interim 12-Month E-FIVE Data**

| 12 Month Outcomes | E-Five (N=1016) | ENDEAVOR Pooled (N=2132) |
|---|---|---|
| | | |
| **MACE** | 6.3% (61/970) | 8.8%(115/1301) |
| | | |
| **Death** | 2.5% (24/970) | 0.9%(12/1301) |
| | | |
| **Cardiac Death** | 1.6% (16/970) | 0.6%(8/1301) |
| | | |
| **Non-cardiac Death** | 0.8% (8/970) | 0.3%(4/1301) |
| | | |
| **Q Wave MI** | 0.4% (4/970) | 0.2%(3/1301) |
| | | |
| **Non Q Wave MI** | 1.1% (11/970) | 2.5%(32/1301) |
| | | |
| **TLR** | 3.3% (32/970) | 5.9%(77/1301) |
| **Stent Thrombosis (Protocol)** | | |
| 30 days | 0.8% (8/1011) | 0.3%(7/2128) |
| 12 months | 1.0% (9/970) | 0.3%(4/1301) |

Finally, while late safety events have been the predominant focus recently for DES, Endeavor shows lower peri-procedural MACE rates as compared to both Cypher (in the ENDEAVOR III trial) and Taxus (in the ENDEAVOR IV trial). Although these trials were not designed to detect these differences, as shown in Table 4-41 and Table 4-42 below, the Endeavor stent produced a six-fold lower frequency of in-hospital MACE compared to the Cypher stent and a three-fold lower frequency compared to the Taxus stent.

**Table 4-41: ENDEAVOR III Peri-Procedural MACE**

| | ENDEAVOR | CYPHER |
|---|---|---|
| In-Hospital MACE | 0.6% (2/323) | 3.5% (4/113) |
| MACE to 30 Days | 0.6% (2/323) | 3.5% (4/113) |

**Table 4-42: ENDEAVOR IV Peri-Procedural MACE**

| | ENDEAVOR | TAXUS |
|---|---|---|
| In-Hospital MACE | 0.9% (7/773) | 2.6% (20/775) |
| MACE to 30 Days | 1.2% (9/770) | 3.0% (23/771) |

In summary, the clinical program has shown that the Endeavor DES is both safe and effective and provides a net patient benefit:

Endeavor significantly reduces the need for repeat revascularization vs. the Driver BMS control and exhibits a long-term clinical efficacy rate that is similar to the currently available DES products.

In addition, the Endeavor stent exhibits an excellent safety profile: the pooled analysis shows low rates of cardiac death, MI, and stent thrombosis vs. the bare metal stent. In addition, the timing of these events has been similar with no apparent increase in these critical events after one year.

The collective evidence provides assurance that Endeavor is both safe and effective.

## 4.6 Conclusion

The Endeavor Zotarolimus-Eluting CSS pre-approval clinical trial program consists of multiple trials in which 2,133 patients were assigned to receive the Endeavor stent, and substantial follow up data is now available: 2,088 patients to 9 months, 1,301 patients to 12 months, 1,287 patients to 24 months, 675 patients to 36 months, and 97 patients to 48 months.

Endeavor's clinical results are complemented by a robust and comprehensive pre-clinical program which concluded that the stents performed as expected in the animal models, without evidence of increased toxicity due to the presence of the drug coating. During the vessel healing process post implant, the Endeavor stent allows for rapid and functional endothelialization with a low and acceptable inflammatory response as shown in pre-clinical studies.

Of the adverse events identified in the Endeavor studies, there was no evidence to suggest potential consequences of immunosuppression, and no laboratory abnormalities attributed to zotarolimus were identified. These results are consistent with excellent tolerability of zotarolimus demonstrated in early intravenous drug safety studies. Zotarolimus pharmacokinetics were characterized in two clinical studies of the Endeavor Zotarolimus-Eluting CSS by low maximum blood concentrations, rapid achievement of the blood maximum concentration, short half-life and rapid clearance of drug from the blood. There was no evidence of dose dumping. In the majority of patients, zotarolimus was not detectable in blood by approximately one to three days following stent placement.

In multiple clinical trials in the US and abroad, the Endeavor stent was shown to be highly deliverable even in patients with highly complex coronary lesions, with higher procedure success rates than the Cypher and Taxus stents in the ENDEAVOR III (99.4% vs. 95.6%) and ENDEAVOR IV trials (98.7% vs. 96.8%), respectively. Clinical performance as assessed by the primary endpoint of Target Vessel Failure was superior to the bare metal Driver stent in the randomized ENDEAVOR II trial and non-inferior to the Taxus stent in the ENDEAVOR IV trial. Based on angiographic endpoints, rates of restenosis were low and consistent across the trials of the Endeavor Zotarolimus-Eluting CSS, and angiographic endpoints for the Endeavor Zotarolimus-Eluting CSS were statistically lower in comparison to the Driver stent. The Endeavor Zotarolimus-Eluting CSS was shown to have a different angiographic profile compared to Cypher and Taxus; however, non-inferiority was clearly demonstrated in ENDEAVOR IV for the endpoint

of 9 month TVF. In all studies, there was no evidence of distal or systemic adverse reactions to the Endeavor Zotarolimus-Eluting CSS, consistent with the minimal, transient systemic exposure to zotarolimus shown in the ENDEAVOR II PK subset and the ENDEAVOR US PK trial. Based on these data, the Endeavor Zotarolimus-Eluting CSS has been shown to consistently provide safe and effective coronary artery stenting, with superior rates of target vessel failure compared to a marketed bare metal stent and non-inferior rates compared to a marketed drug eluting stent.

# EXHIBIT G

UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

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MEETING

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THURSDAY,
NOVEMBER 29, 2007

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The meeting convened at 8:00 a.m. at the Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, Maryland, CLYDE W. YANCY, M.D., Acting Panel Chairperson, presiding.

PANEL MEMBERS PRESENT:

CLYDE YANCY, M.D, Acting Chairperson
RICHARD L. PAGE, M.D., Voting Member
JOHN C. SOMBERG, M.D., Voting Member
EUGENE H. BLACKSTONE, M.D., Consultant
JEFFREY A. BRINKER, M.D., Consultant
JOHN W. HIRSHFELD, M.D., Consultant
VALLUVAN JEEVANANDAM, M.D., Consultant
NORMAN S. KATO, M.D., Consultant
WARREN K. LASKEY, M.D., Consultant
DOUGLAS MORRISON, M.D., Consultant
SHARON-LISE NORMAND, Ph.D., Consultant
MARCIA S. YAROSS, Ph.D., Industry Representative
KAREN R. RUE, Consumer Representative

all possibilities based on the anatomy.

DR. NORMAND: Because that's an important point I would raise, a very strong aspect of your study, if they, generally -- if it is true that they agreed, sort of I'll sign up, and wherever I go, is wherever I'll go. That's what you've just basically said, and that's actually very powerful in terms of applicability for that particular arm.

DR. STONE: Well, that is how it happened. And those were mutually exclusive decisions. You couldn't qualify for both.

DR. NORMAND: Exactly. Thank you.

DR. YANCY: Let me pose a question to Dr. Hirshfeld, and then a question, perhaps, to the sponsor. In your matrix, you position the efficacy at a point that I think we would all agree with your assessment, inclining towards similar or even better than TAXUS, but on the safety issue, you used a phrase "not sufficient data and some ambiguity". Could you articulate that better?

And, specifically, are you commenting on the absence of the very late thrombosis data, or do you have some other concerns?

DR. HIRSHFELD: Well, I was deliberately brief, because I didn't want to take up too much time. But, basically, if you look at the various components of MACE, they go in different directions. Some of them, I think, are linked to the effectiveness of the drug, of this device of preventing restenosis. However, there clearly is no decrease in stent thrombosis, and depending upon which data set you look at, and how you examine it, it's possible that this device might have a greater frequency of stent thrombosis than some other devices. I think there's just not enough data at the moment to look at.

And then when you say well, what is MACE? Well, MACE actually is MACE with a lower case M-A-C-E, and then there is MACE with a big, bold upper case M-A-C-E, such as stent thrombosis, and anterior ST elevation

MIs. So that's why I think that if you look at the data now, there are some suggestions that it has fewer adverse events in some axes, and has either comparable, or possibly more adverse events in other axes. And I think it's not possible to take the data any further than that, until there are more data that have become available.

DR. YANCY: So perhaps the sponsor can just help us maybe just with perspective here, because I think Dr. Morrison finished his comments with a fairly powerful statement about the paucity of long-term follow-up data. And Dr. Somberg challenged the availability of more data referable to a long-term endpoint. And Dr. Hirshfeld is building some of that into his concerns about MACE, small case or upper case. And so, obviously, a strategic decision was made to come forward with the database as it exists with the awareness that there was not the kind of robust long-term information that some on the

DR. NORMAND: I voted for approval with conditions, because the sponsor showed effectiveness with a reasonable sample size for the clinical endpoint. The late loss was based on a much smaller sample size, and so I rested more of my weight towards the clinical endpoint.

With regard to safety, I had no prior reason to believe there would be a safety issue. The data that were demonstrated did not show there was a safety issue, and hence, my reason for voting for approvable with conditions.

DR. YANCY: Dr. Somberg.

DR. SOMBERG: Well, I voted against approval. I thought the safety data in the 12 to 24 months was inadequate, and it was a bad precedent to establish, and I thought with the pivotal study only contributing, or having not been fully evaluated, and only contributing 35 percent to the numbers, it was of concern to me in that with the recent tumult about late

stent thrombosis, which may or may not be a real issue, to have inadequate data leaves this issue really unaddressed for many years to resolve.

DR. YANCY: Dr. Laskey.

DR. LASKEY: I voted for approval. The study met it's pre-specified endpoints on both counts out to one year in terms of safety. We discussed that, so the condition for approval reflects that with prolonged follow-up, and a post-approval registry. And, finally, there's something very gratifying about returning to an earlier form of technology which works very well, which is the thin strut. The data was always there before, and it's nice to see it reflected again.

DR. YANCY: Dr. Page.

DR. PAGE: I voted in favor of approvable with the conditions as outlined. I feel that reasonable assurance of safety was demonstrated, as well as reasonable assurance of effectiveness, and even advantage. And I